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# Thirty Years of Evidence on the Efficacy of Drug Treatments for Chronic Heart Failure With Reduced Ejection Fraction

## A Network Meta-Analysis

Heather Burnett, MSc; Amy Earley, BSc; Adriaan A. Voors, MD, PhD; Michele Senni, MD; John J.V. McMurray, MD; Celine Deschaseaux, MSc; Shannon Cope, MSc

***Background***—Treatments that reduce mortality and morbidity in patients with heart failure with reduced ejection fraction, including angiotensin-converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB), β-blockers (BB), mineralocorticoid receptor antagonists (MRA), and angiotensin receptor–neprilysin inhibitors (ARNI), have not been studied in a head-to-head fashion. This network meta-analysis aimed to compare the efficacy of these drugs and their combinations regarding all-cause mortality in patients with heart failure with reduced ejection fraction.

***Methods and Results***—A systematic literature review identified 57 randomized controlled trials published between 1987 and 2015, which were compared in terms of study and patient characteristics, baseline risk, outcome definitions, and the observed treatment effects. Despite differences identified in terms of study duration, New York Heart Association class, ejection fraction, and use of background digoxin, a network meta-analysis was considered feasible and all trials were analyzed simultaneously. The random-effects network meta-analysis suggested that the combination of ACEI+BB+MRA was associated with a 56% reduction in mortality versus placebo (hazard ratio 0.44, 95% credible interval 0.26–0.66); ARNI+BB+MRA was associated with the greatest reduction in all-cause mortality versus placebo (hazard ratio 0.37, 95% credible interval 0.19–0.65). A sensitivity analysis that did not account for background therapy suggested that ARNI monotherapy is more efficacious than ACEI or ARB monotherapy.

***Conclusions***—The network meta-analysis showed that treatment with ACEI, ARB, BB, MRA, and ARNI and their combinations were better than the treatment with placebo in reducing all-cause mortality, with the exception of ARB monotherapy and ARB plus ACEI. The combination of ARNI+BB+MRA resulted in the greatest mortality reduction. **(*Circ Heart Fail*. 2017;10:e003529. DOI: 10.1161/CIRCHEARTFAILURE.116.003529.)**

**Key Words:** drug combinations ■ drug therapy ■ heart failure ■ mortality ■ network meta-analysis



Mortality in patients with heart failure and reduced ejection fraction (HFrEF) has improved over time because of the step-wise introduction of a variety of pharmacological treatments. For years, recommended treatments for patients with HFrEF included the combination of an angiotensin-converting enzyme inhibitor (ACEI; or an angiotensin II receptor blocker [ARB] if an ACEI is not tolerated), a β-blocker (BB), and a mineralocorticoid receptor antagonist (MRA).[1] Despite these recommended treatments being evidence based, the mortality rate for patients with HFrEF remains high.[2–4]

Sacubitril/valsartan, a first-in-class angiotensin receptor–neprilysin inhibitor (ARNI), was recommended as a new treatment option for patients with HFrEF in the 2016 European Society for Cardiology guidelines[5] and the 2016 American College of Cardiology/American Heart Association guidelines.[6] These recommendations were based on the results of the PARADIGM-HF trial (Prospective Comparison of ARNI With ACE to Determine Impact on Global Mortality and Morbidity in Heart Failure), which showed sacubitril/valsartan to be superior to enalapril in reducing the risks of cardiovascular and all-cause mortality when added to a BB (in most patients) and a MRA (in many), as well as a diuretic and digoxin.[7]

**See Clinical Perspective**

There are now 5 types (ACEI, ARB, BB, MRA, and ARNI) of life-saving pharmacological therapies available to treat patients with HFrEF. Given that most trials in HFrEF have compared newer agents to placebo, which has included alternative background treatments as recommendations have evolved, there is a need to understand how the efficacy of these individual treatments and various combinations compare in

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From the Mapi, Health Economics and Outcomes Research, Dundas, Canada (H.B.); Mapi, Health Economics and Outcomes Research, Boston, MA (A.E.); Department of Cardiology, University of Groningen, The Netherlands (A.A.V.); Cardiovascular Department, Hospital Papa Giovanni XXIII, Bergamo, Italy (M.S.); British Heart Foundation Cardiovascular Research Centre, University of Glasgow, UK (J.J.V.M.); Global Patient Access, Novartis Pharma AG, Postfach, CH-4002 Basel, Switzerland (C.D.); and Mapi, Health Economics and Outcomes Research, Toronto, Canada (S.C.).

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Correspondence to Heather Burnett, MSc, 4 Innovation Dr, Dundas, Ontario L9H 7P3, Canada. E-mail hburnett@mapigroup.com

terms of all-cause mortality. If all trials have at least one intervention in common with another, it is possible to develop a network of randomized controlled trials (RCTs), allowing for indirect comparisons of interventions not studied in a head-to-head fashion using network meta-analysis (NMA).[8] The validity of any NMA relies on whether there are systematic differences across RCTs in terms of patient or disease characteristics that are treatment effect modifiers.[8–11] Consequently, it is important to identify the relevant network of RCTs and to assess the feasibility of performing a valid NMA.

The objective of this study was to systematically identify RCTs evaluating recommended drug classes and combinations for HFrEF in terms of all-cause mortality and to perform a valid NMA assessing the comparative efficacy of these therapies.

## Methods

### Identification and Selection of Studies

A systematic literature review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[12] Medline, EMBASE, and Cochrane CENTRAL were searched to identify studies published between January 1987 and April 28, 2015. Search terms included a combination of free text and Medical Subject Heading terms (see Data Supplement). Two reviewers (H. Burnett and A. Earley) independently screened citations against the following predefined selection criteria.

#### *Population*

Studies evaluating adults (aged ≥18 years) with chronic HFrEF (left ventricular ejection fraction <45%) and New York Heart Association class II–IV of varying etiology (ischemic and dilated cardiomyopathy) who were outpatients were included. Studies were excluded if the entire study population had one of the following characteristics, which are known to impact treatment response or all-cause mortality: (1) acute heart failure, (2) hospitalized, (3) New York Heart Association class I, (4) clinical comorbidity (eg, chronic obstructive pulmonary disease, diabetes mellitus, or renal failure), (5) coronary heart disease, (6) post-myocardial infarction, (7) ischemia, (8) idiopathic dilated cardiomyopathy, (9) elderly (aged >70 years), or (10) from country outside of North America or Europe. Studies that included a proportion of patients with the characteristics described above were included.

#### *Interventions*

All guideline-recommended drug classes: ACEIs, BBs, ARBs, and MRAs and an ARNI, administered alone or in combination (see Table I in the Data Supplement for eligible drug molecules).

#### *Comparators*

Placebo or any intervention of interest of a different class; comparisons within the same class were excluded (eg, ACEI versus ACEI).

#### *Outcomes*

Death because of any cause reported as an efficacy or safety end point.

#### *Study Design*

Phase II or III RCTs published in English.

### Data Extraction and Quality Assessment

For each included study, details were extracted on study design, patient characteristics, and interventions. The quality of the RCTs was assessed.[13] For all-cause mortality, the total number of events was extracted for each arm, and the exposure time for each trial was extracted for the planned study duration, if reported, or else the mean or median follow-up time.

### Feasibility Assessment

The feasibility of conducting a valid NMA was assessed using the process described by Cope et al,[14] which involves an assessment of clinical heterogeneity in terms of the characteristics of the treatments, outcomes, study design, and patients and a comparison of

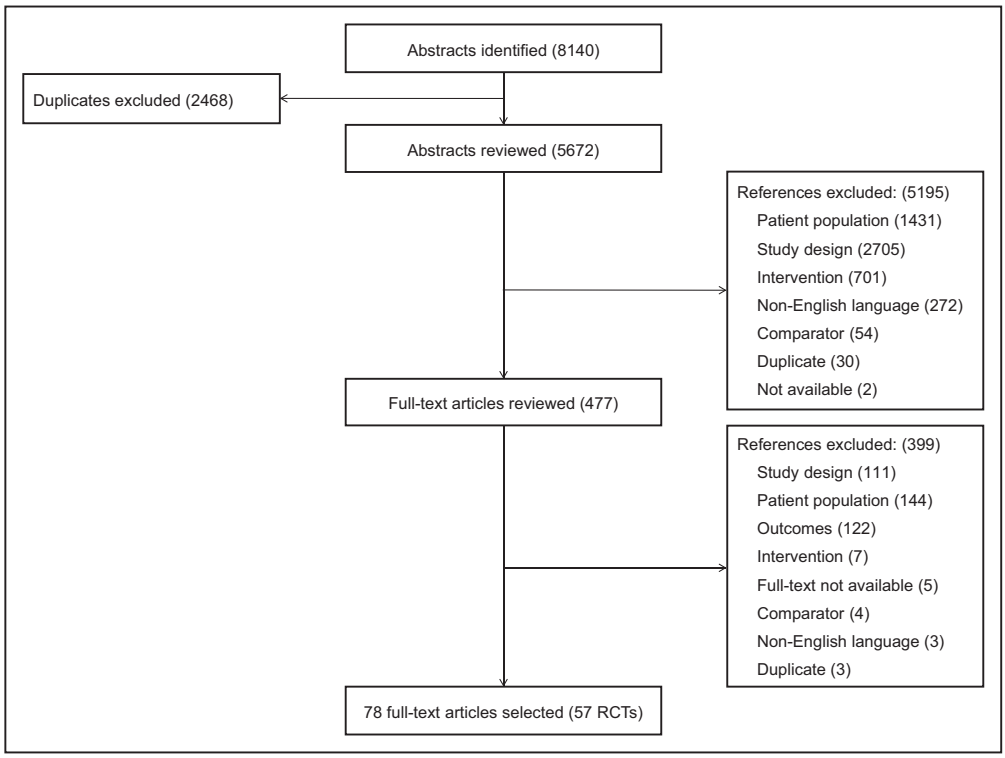


**Figure 1.** Flow diagram. RCT indicates randomized controlled trials.

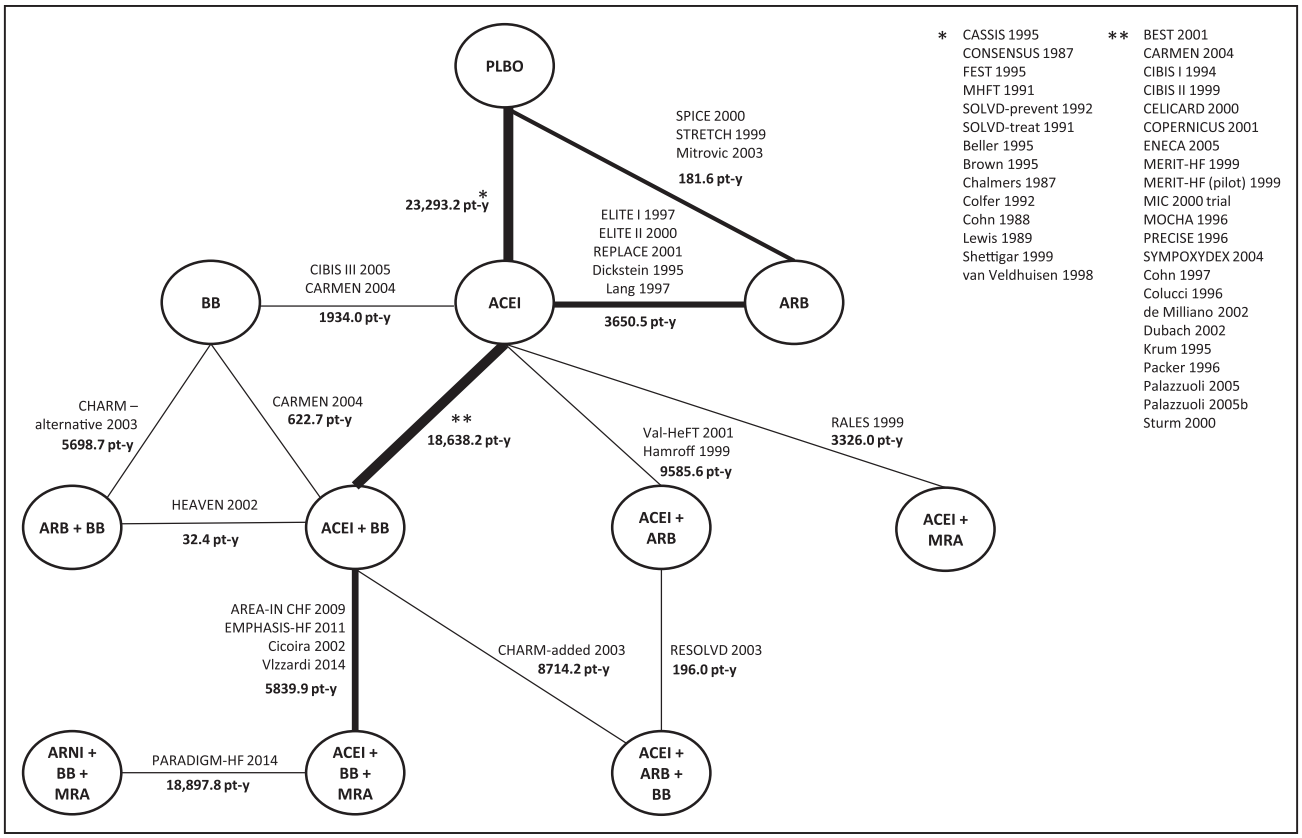


**Figure 2.** Network diagram of treatment classes and combinations reporting all-cause mortality. ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin-II receptor blocker; AREA-IN CHF, Anti-Remodelling Effect of Canrenone in Patients With Mild Chronic Heart Failure; ARNI, angiotensin receptor-neprilysin inhibitor; BB, beta blocker; BEST, Beta-Blocker Evaluation of Survival Trial; CARMEN, The Carvedilol and ACE-Inhibitor Remodelling Mild Heart Failure Evaluation Trial; CASSIS, Czech and Slovak Spirapril Intervention Study; CHARM-added, Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity–Added; CHARM-alternative, Candesartan in Heart Failure–Assessment of Mortality and Morbidity Alternative; CIBIS, Cardiac Insufficiency Bisoprolol Study; CONSENSUS, Cooperative North Scandinavian Enalapril Survival Study; COPERNICUS, Carvedilol Prospective Randomized Cumulative Survival; ELITE, Evaluation of Losartan in the Elderly Study; EMPHASIS-HF, Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure; ENECA, Efficacy of Nebivolol in the Treatment of Elderly Patients With Chronic Heart Failure as Add-On Therapy to ACE Inhibitors or Angiotensin II Receptor Blockers, Diuretics, and/or Digitalis; FEST, Fosinopril Efficacy/Safety Trial; HEAVEN, Heart Failure Valsartan Exercise Capacity Evaluation; MERIT-HF, Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure; MHFT, Munich Mild Heart Failure Trial; MIC, Metoprolol in Patients With Mild to Moderate Heart Failure: Effects on Ventricular Function and Cardiopulmonary Exercise Testing; MOCHA, Multicenter Oral Carvedilol Heart Failure Assessment; MRA, mineralocorticoid receptor antagonist; PARADIGM-HF, Prospective Comparison of ARNI (Angiotensin Receptor–Neprilysin Inhibitor) With ACEI (Angiotensin–Converting–Enzyme Inhibitor) to Determine Impact on Global Mortality and Morbidity in Heart Failure; PLBO, placebo; PRECISE, Prospective Randomized Evaluation of Carvedilol on Symptoms and Exercise; RALES, Randomized Aldactone Evaluation Study; REPLACE, Replacement of Angiotensin Converting Enzyme Inhibition; RESOLVD, Randomized Evaluation of Strategies for Left Ventricular Dysfunction; SOLVD-prevent, Studies of Left Ventricular Dysfunction–Prevention Trial; SOLVD-treat, Studies of Left Ventricular Dysfunction–Treatment Trial; SPICE, Study of Patients Intolerant of Converting Enzyme Inhibitors; STRETCH, Symptom, Tolerability, Response to Exercise Trial of Candesartan Cilexetil in Heart Failure; SYMPOXYDEX, Sympathetic and Oxydative Stress Kredex Study; and Val-HeFT, Valsartan Heart Failure Trial.[7,21–77]

differences within and across treatments in terms of baseline risk and the observed treatment effects. The following factors were identified a priori as potential treatment effect modifiers: use of concomitant treatments (eg, digoxin), duration of follow-up, year of publication, severity of included patients (eg, New York Heart Association class and left ventricular ejection fraction), heart failure etiology (eg, ischemic versus nonischemic), and history of myocardial infarction.

## Network Meta-Analysis

Bayesian NMA models were used to simultaneously synthesize the results of the included studies and to obtain relative treatment effects.[11,15–17] NMA within the Bayesian framework involves data, a hierarchical model or likelihood function with parameters, and prior distributions.[18] The model relates data from RCTs to parameters reflecting the (pooled) relative treatment effect of each intervention compared with the reference treatment (eg, placebo). Data sets for the model were based on the reported number of patients with an event at the end of the trial per arm, the total number of patients randomized per arm, and the mean follow-up duration of the trial. The log mean follow-up time was used to transform the probability of an event into a constant rate for each trial arm by assuming an underlying Poisson process, and a complementary log–log (cloglog) link was used to model the event rates.[10] Outputs from the model were presented as hazard ratios (HRs) for each treatment versus placebo. Goodness of fit was assessed using the residual deviance and deviance information criterion.[19] Results of the random-effects model were presented unless the fixed-effect model resulted in a more parsimonious model. Noninformative prior distributions were used: a normal distribution for the difference measures (mean 0, var $10^4$) and a uniform distribution for between-study standard deviation (range 0–5). The analysis was performed with published codes[10] using OpenBuGS software[20] (2 chains were used, including 100 000 burn-in iterations followed by 200 000 iterations).

Results of the NMA reflect the posterior distributions of the model parameters. In addition to point estimates of the HRs, 95% credible intervals (CrI), reflecting the range of true underlying effects with

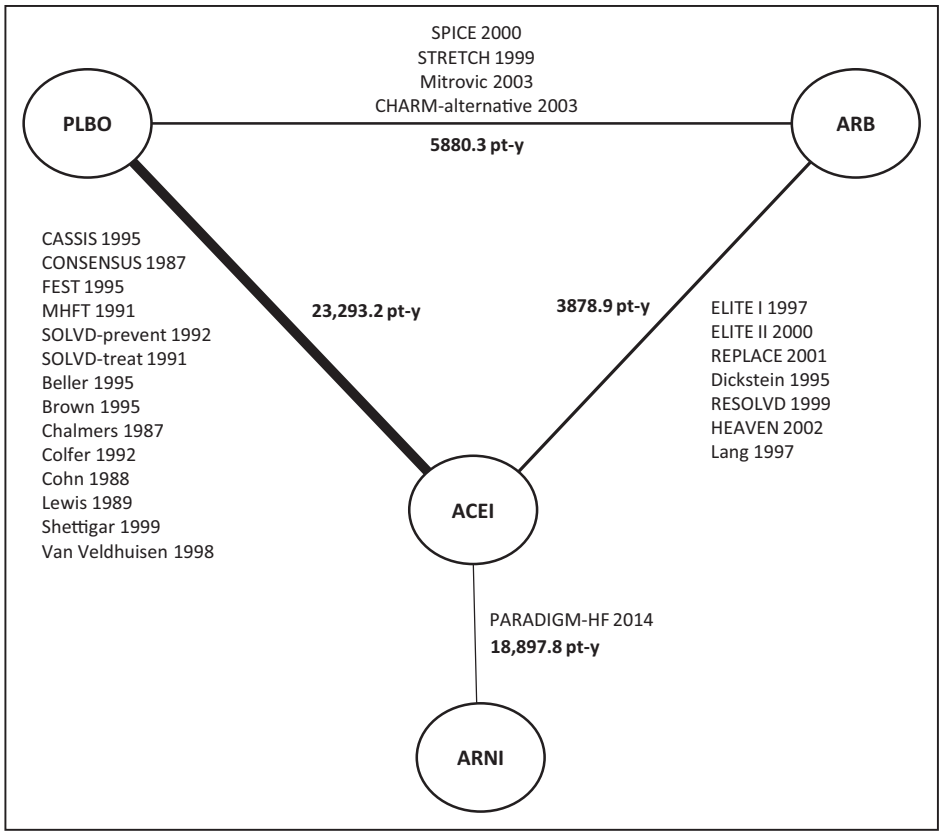


**Figure 3.** Sensitivity analysis evidence network of ARNI, ACEI, ARB and placebo for all-cause mortality ignoring background treatments. ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin-II receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; CASSIS, Czech and Slovak Spirapril Intervention Study; CHARM-alternative, Candesartan in Heart Failure–Assessment of Mortality and Morbidity Alternative; CONSENSUS, Cooperative North Scandinavian Enalapril Survival Study; ELITE, Evaluation of Losartan in the Elderly Study; FEST, Fosinopril Efficacy/Safety Trial; HEAVEN, Heart Failure Valsartan Exercise Capacity Evaluation; MHFT, Munich Mild Heart Failure Trial; PARADIGM-HF, Prospective Comparison of ARNI (Angiotensin Receptor–Neprilysin Inhibitor) With ACEI (Angiotensin–Converting–Enzyme Inhibitor) to Determine Impact on Global Mortality and Morbidity in Heart Failure; PLBO, placebo; REPLACE, Replacement of Angiotensin Converting Enzyme Inhibition; RESOLVD, Randomized Evaluation of Strategies for Left Ventricular Dysfunction; SOLVD-prevent, Studies of Left Ventricular Dysfunction–Prevention Trial; SOLVD-treat, Studies of Left Ventricular Dysfunction–Treatment Trial; SPICE, Study of Patients Intolerant of Converting Enzyme Inhibitors; and STRETCH, Symptom, Tolerability, Response to Exercise Trial of Candesartan Cilexetil in Heart Failure.[7,21–45]

95% probability, are presented. The rank probabilities and expected rank for all treatments are presented, as well as the probability that one treatment is better than a specific comparator.[11] Means, standard deviations, and ranges were summarized for study and patient characteristics where possible.

# Results

## Study Selection

Fifty-seven RCTs were included (Figure 1) and are described in Table II in the Data Supplement.[7,21–77] The majority were multicenter, double-blind, placebo-controlled trials, including between 28 and 8399 patients with a mean follow-up duration ranging from 8 weeks to 4 years. The treatment classes assessed included ACEI, BB, ARB, MRA, and ARNI. Patients were generally allowed concomitant therapies, such as diuretics, digoxin, and nitrates, as well as other permitted concomitant treatment classes.

## Network of Evidence

In the network of connected RCTs (Figure 2), the thickness of the lines corresponds to the number of trials included per treatment comparison. The evidence was centralized around placebo and ACEI, with most RCTs informing the comparison of ACEI+BB versus ACEI. The treatment combination with ARNI was informed by a single RCT.

## Differences Within or Between Direct Treatment Comparisons That May Modify Treatment Effect

### *Treatment Definitions*

There was a wide range in the types of individual and concomitant treatments (Table III in the Data Supplement). In fact, few trials included a true placebo arm because study patients were often permitted to receive or continue to receive the standard of care in addition to study drugs. An increase in the use of combination therapies was observed over the years, with the earliest trials being focused on ACEIs versus placebo, followed by the addition of BB (ACEI+BB versus ACEI studies), and then ARB and MRA containing therapies around the same time after their introduction. The combination ACEI+BB+MRA was first evaluated in 2002 compared with ACEI+BB. To take into account concomitant drug classes of interest and more accurately define placebo in the analysis, treatments were categorized to include the concomitant drug when the majority of

patients in the study were receiving it at baseline. Specifically, if >50% of the trial patients received a concomitant drug of interest in the systematic review (eg, BB), the treatment was described as a combination therapy (the study drug class+the concomitant drug class(es), eg, ACEI+BB versus BB) in the analysis. The threshold to define concomitant therapy was based on expert opinion and involved an evaluation of different thresholds ranging from 50% to 60%.[78]

When the permitted concomitant drug was ACEI or ARB and the publication failed to report the distribution of patients receiving each class, it was assumed that patients were taking ACEI (Table IV in the Data Supplement). A sensitivity

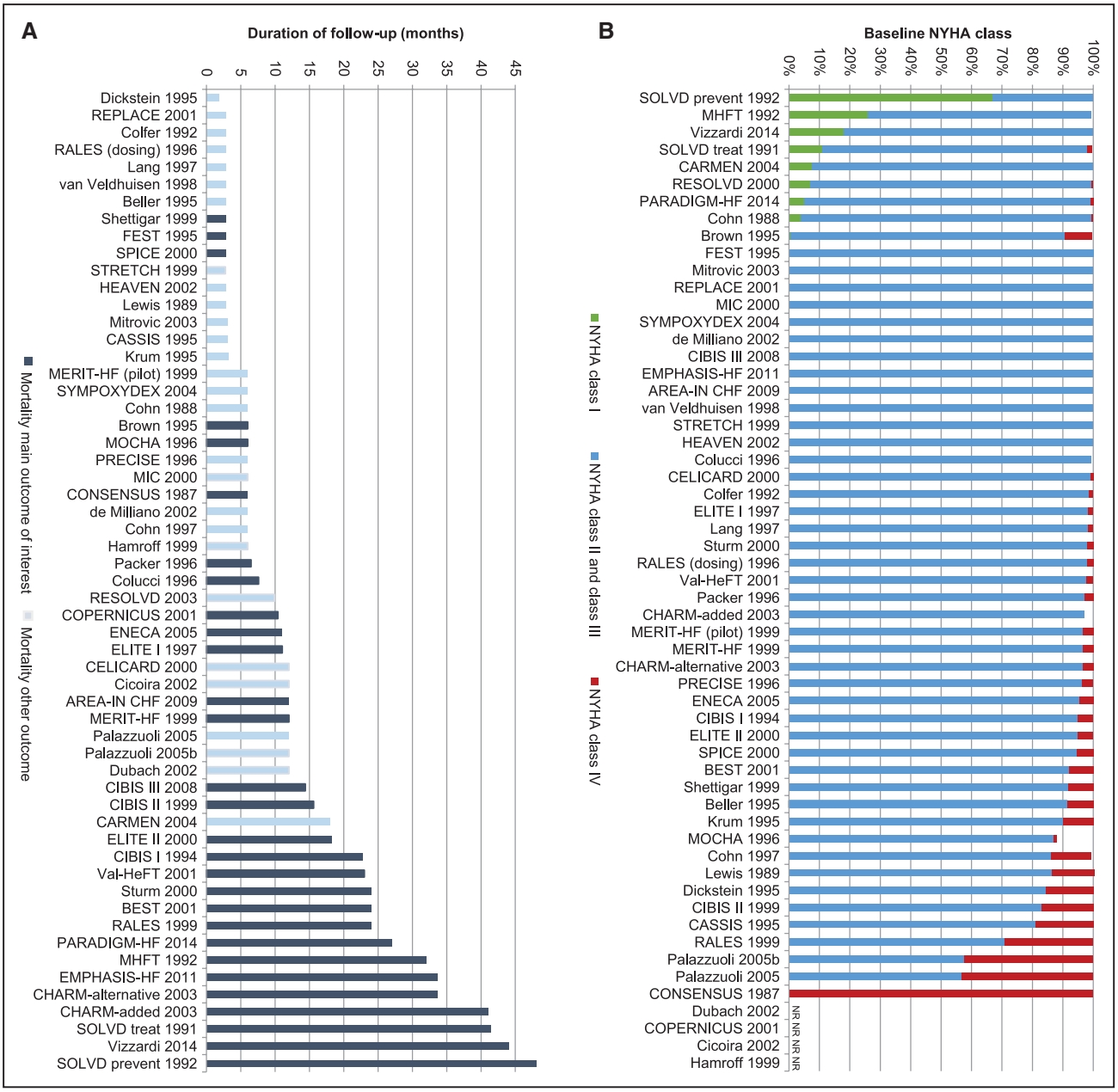


**Figure 4.** Distribution of potential treatment effect modifiers: **A**, Duration of follow-up[7,21–77]; **B**, NYHA class at baseline[7,21–77]; **C**, LVEF at baseline.[7,21–77] AREA-IN CHF indicates Anti-Remodelling Effect of Canrenone in Patients With Mild Chronic Heart Failure; BEST, Beta-Blocker Evaluation of Survival Trial; CARMEN, The Carvedilol and ACE-Inhibitor Remodelling Mild Heart Failure Evaluation Trial; CASSIS, Czech and Slovak Spirapril Intervention Study; CHARM-added, Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity–Added; CHARM-alternative, Candesartan in Heart Failure–Assessment of Mortality and Morbidity Alternative; CIBIS, Cardiac Insufficiency Bisoprolol Study; CONSENSUS, Cooperative North Scandinavian Enalapril Survival Study; COPERNICUS, Carvedilol Prospective Randomized Cumulative Survival; ELITE, Evaluation of Losartan in the Elderly Study; EMPHASIS-HF, Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure; ENECA, Efficacy of Nebivolol in the Treatment of Elderly Patients With Chronic Heart Failure as Add-On Therapy to ACE Inhibitors or Angiotensin II Receptor Blockers, Diuretics, and/or Digitalis; FEST, Fosinopril Efficacy/Safety Trial; HEAVEN, Heart Failure Valsartan Exercise Capacity Evaluation; LVEF, left ventricular ejection fraction; MERIT-HF, Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure; MHFT, Munich Mild Heart Failure Trial; MIC, Metoprolol in Patients With Mild to Moderate Heart Failure: Effects on Ventricular Function and Cardiopulmonary Exercise Testing; MOCHA, Multicenter Oral Carvedilol Heart Failure Assessment; NR, not reported; NYHA, New York Heart Association; PARADIGM-HF, Prospective (*Continued*)

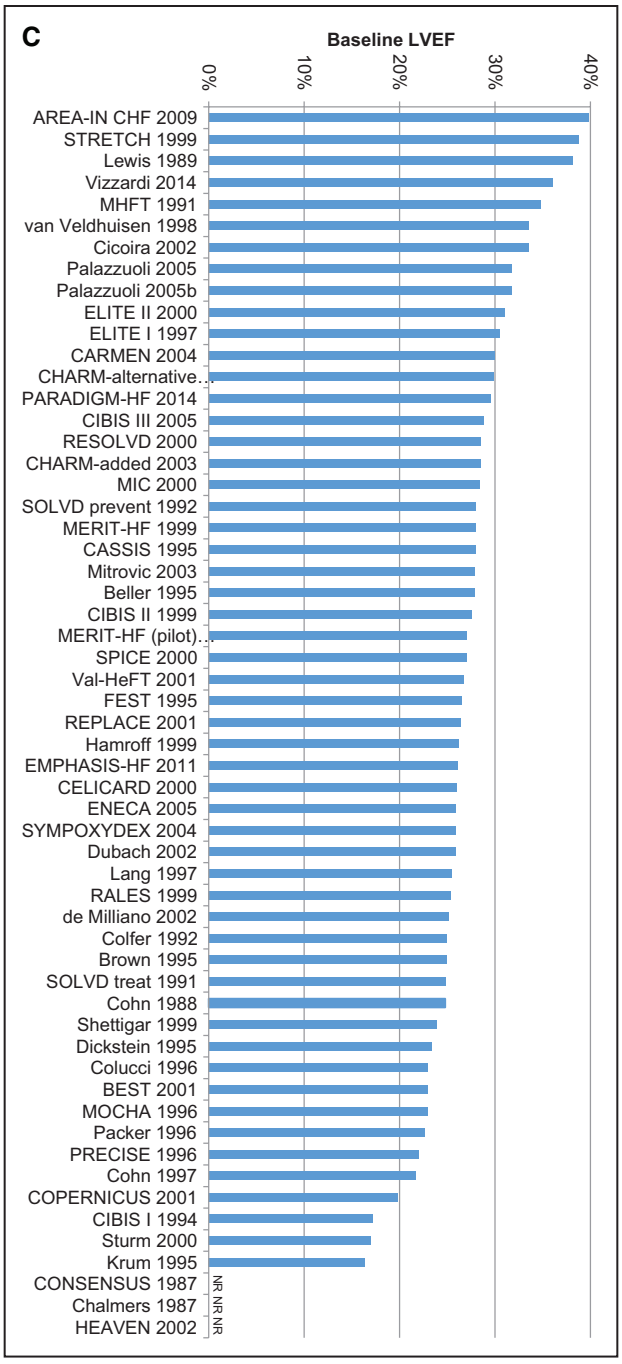


**Figure 4 Continued.** Comparison of ARNI (Angiotensin Receptor–Neprilysin Inhibitor) With ACEI (Angiotensin–Converting–Enzyme Inhibitor) to Determine Impact on Global Mortality and Morbidity in Heart Failure; PRECISE, Prospective Randomized Evaluation of Carvedilol on Symptoms and Exercise; RALES, Randomized Aldactone Evaluation Study; REPLACE, Replacement of Angiotensin Converting Enzyme Inhibition; RESOLVD, Randomized Evaluation of Strategies for Left Ventricular Dysfunction; SOLVD-prevent, Studies of Left Ventricular Dysfunction–Prevention Trial; SOLVD-treat, Studies of Left Ventricular Dysfunction–Treatment Trial; SPICE, Study of Patients Intolerant of Converting Enzyme Inhibitors; STRETCH, Symptom, Tolerability, Response to Exercise Trial of Candesartan Cilexetil in Heart Failure; SYMPOXYDEX, Sympathetic and Oxydative Stress Kredex Study; and Val-HeFT, Valsartan Heart Failure Trial.

analysis was also performed that ignored concomitant therapies and evaluated how ARNI monotherapy was compared with ACEI and ARB monotherapies (Figure 3).[7,21–45]

Despite some variation in individual treatment doses and schedules (Table V in the Data Supplement), all analyses assumed that treatments within a given class were comparable in terms of their ability to prevent death. All trials were included, even though some variation was also observed in the proportion of patients receiving concomitant digoxin.

### *Outcome Definition*

All-cause mortality is an objective end point and is usually reported as a primary or secondary outcome, although the NMA also included 28 trials that reported mortality as an adverse event or a reason for study withdrawal (Figure 4A). Because the quality of these 28 studies did not differ greatly from that of the other included trials, the broadest evidence base was included.

### *Study and Patient Characteristics*

The RCTs were broadly comparable in terms of study design, despite a wide range in publication year (1987–2014). There were some differences in study quality, although overall the risk of bias was low (Figure I in the Data Supplement). Given the differences in the duration of follow-up across trials (Figure 4A), patient exposure was accounted for in the analysis.

Enrolled patients were predominantly male (mean 76%, range 49%–90%) and between the ages of 52 and 73 years (mean 62 years; Table II in the Data Supplement). Most patients were classified as New York Heart Association class II–III (mean 86%), although 8 (14%) trials included a proportion of patients in class I and 36 (63%) trials included patients in class IV (Figure 4B). Baseline left ventricular ejection fraction ranged between 15% and 40% (mean 27%; Figure 4C). In terms of heart failure etiology, 57% of the included patients had ischemic heart disease (range 10%–83%). It was not possible to consistently assess differences in the duration of heart failure, the use of pacemakers or implantable devices, or the history of myocardial infarction because of inconsistent reporting.

### *Baseline Risk and Observed Treatment Effects*

Given variation in publication year across trials, differences attributable to changes in clinical practice over time may result in differences in baseline risk that could influence the treatment effect. However, the network of evidence does not provide a well-connected common comparator (placebo or standard of care), partly because of the treatment categorization based on concomitant therapy used to account for differences in placebo. Figure II in the Data Supplement reports the rates of death per patient year for all treatment arms and RCTs by publication year. Although the rates varied across included RCTs, it was unclear whether these differences were driven by changes in practice over time or acted as a treatment effect modifier.

## Network Meta-Analysis Results

All identified RCTs were included in the NMA and provided comparative evidence on all-cause mortality in patients with HFrEF.

**Table 1. Results of Random Effect Network Meta-Analysis for All-Cause Mortality Rates: Difference in Intervention Versus the Comparator, 95% Credible Intervals (CrI), and Probability That the Intervention Is Better Than the Comparator [*P*(better)]**

| | Comparator | | | | |
|---|---|---|---|---|---|
| Intervention | PLBO | ACEI | ARB | BB | ACEI+BB |
| PLBO | | | | | |
| Estimate (95% CrI) | 1 (1,1) | 1.203 (0.989–1.512) | 1.132 (0.793–1.65) | 1.752 (1.067–3.041) | 1.758 (1.382–2.424) |
| *P*(better) | NA | 0.03 | 0.23 | 0.01 | 0.00 |
| ACEI | | | | | |
| Estimate (95% CrI) | 0.831 (0.661–1.011) | 1 (1–1) | 0.941 (0.679–1.292) | 1.454 (0.92–2.38) | 1.462 (1.255–1.783) |
| *P*(better) | 0.97 | NA | 0.66 | 0.05 | 0.00 |
| ARB | | | | | |
| Estimate (95% CrI) | 0.883 (0.606–1.261) | 1.063 (0.774–1.473) | 1 (1–1) | 1.548 (0.886–2.8) | 1.552 (1.103–2.31) |
| *P*(better) | 0.77 | 0.34 | NA | 0.06 | 0.01 |
| BB | | | | | |
| Estimate (95% CrI) | 0.571 (0.329–0.937) | 0.688 (0.42–1.087) | 0.646 (0.357–1.129) | 1 (1–1) | 1.008 (0.615–1.633) |
| *P*(better) | 0.99 | 0.95 | 0.94 | NA | 0.49 |
| ACEI+BB | | | | | |
| Estimate (95% CrI) | 0.569 (0.413–0.724) | 0.684 (0.561–0.797) | 0.644 (0.433–0.906) | 0.992 (0.612–1.626) | 1 (1–1) |
| *P*(better) | 1.0 | 1.0 | 0.99 | 0.51 | NA |
| ACEI+ARB | | | | | |
| Estimate (95% CrI) | 0.827 (0.505–1.243) | 0.994 (0.658–1.448) | 0.935 (0.548–1.514) | 1.441 (0.789–2.672) | 1.448 (0.964–2.232) |
| *P*(better) | 0.84 | 0.52 | 0.62 | 0.11 | 0.03 |
| ARB+BB | | | | | |
| Estimate (95% CrI) | 0.472 (0.23–0.855) | 0.567 (0.293–1.002) | 0.534 (0.254–1.021) | 0.828 (0.518–1.215) | 0.831 (0.435–1.493) |
| *P*(better) | 0.99 | 0.97 | 0.97 | 0.85 | 0.74 |
| ACEI+MRA | | | | | |
| Estimate (95% CrI) | 0.574 (0.348–0.908) | 0.69 (0.448–1.058) | 0.648 (0.378–1.103) | 1.003 (0.54–1.935) | 1.004 (0.653–1.649) |
| *P*(better) | 0.99 | 0.96 | 0.95 | 0.50 | 0.49 |
| ACEI+ARB+BB | | | | | |
| Estimate (95% CrI) | 0.518 (0.308–0.795) | 0.623 (0.397–0.926) | 0.586 (0.334–0.97) | 0.903 (0.486–1.68) | 0.908 (0.614–1.358) |
| *P*(better) | 1.0 | 0.99 | 0.98 | 0.64 | 0.72 |
| ACEI+BB+MRA | | | | | |
| Estimate (95% CrI) | 0.44 (0.264–0.661) | 0.53 (0.342–0.762) | 0.498 (0.286–0.804) | 0.767 (0.417–1.397) | 0.773 (0.535–1.091) |
| *P*(better) | 1.0 | 1.0 | 1.0 | 0.81 | 0.94 |
| ARNI+BB+MRA | | | | | |
| Estimate (95% CrI) | 0.372 (0.189–0.647) | 0.448 (0.24–0.758) | 0.421 (0.206–0.774) | 0.648 (0.308–1.329) | 0.652 (0.371–1.11) |
| *P*(better) | 1.0 | 1.0 | 0.99 | 0.89 | 0.95 |

(*Continued*)

Table 1 presents the results of the random effect NMA for all head-to-head comparisons and illustrates the HRs, the 95% CrIs, and the probability of a treatment being better than the comparator. We found significant between-study heterogeneity in the network of evidence (SD 0.18, 95% CrI 0.06–0.35; Table 1), which was expected given the differences observed in the included studies.

Figure 5 illustrates the HRs for each treatment class versus placebo for all-cause mortality. The combination of ACEI+BB+MRA was associated with a 56% reduction in mortality versus placebo (HR 0.44, 95% CrI 0.26–0.66), while ARNI+BB+MRA was associated with the greatest reduction in all-cause mortality versus placebo (HR 0.37, 95% CrI 0.19–0.65). Figure III in the Data Supplement summarizes the rank probabilities for all interventions.

Table 2 presents the results from the sensitivity analysis that ignored concomitant therapies and evaluated how ARNI monotherapy was compared with ACEI and ARB monotherapies. The random-effects model suggests that all active treatments are

**Table 1. Continued**

| Intervention | Comparator | | | | | |
|---|---|---|---|---|---|---|
| | ACEI+ARB | ARB+BB | ACEI+MRA | ACEI+ARB+BB | ACEI+BB+MRA | ARNI+BB+MRA |
| PLBO | | | | | | |
| Estimate (95% CrI) | 1.21 (0.804–1.979) | 2.121 (1.169–4.354) | 1.744 (1.101–2.874) | 1.929 (1.258–3.244) | 2.272 (1.513–3.791) | 2.689 (1.545–5.303) |
| *P*(better) | 0.16 | 0.01 | 0.01 | 0.00 | 0.00 | 0.00 |
| ACEI | | | | | | |
| Estimate (95% CrI) | 1.007 (0.691–1.521) | 1.763 (0.998–3.415) | 1.45 (0.945–2.232) | 1.605 (1.08–2.518) | 1.889 (1.312–2.925) | 2.235 (1.319–4.166) |
| *P*(better) | 0.48 | 0.03 | 0.04 | 0.01 | 0.00 | 0.00 |
| ARB | | | | | | |
| Estimate (95% CrI) | 1.07 (0.66–1.824) | 1.871 (0.98–3.945) | 1.542 (0.907–2.645) | 1.707 (1.031–2.997) | 2.009 (1.243–3.501) | 2.378 (1.291–4.847) |
| *P*(better) | 0.38 | 0.03 | 0.05 | 0.02 | 0.00 | 0.01 |
| BB | | | | | | |
| Estimate (95% CrI) | 0.694 (0.374–1.267) | 1.207 (0.823–1.929) | 0.997 (0.517–1.852) | 1.107 (0.595–2.058) | 1.304 (0.716–2.398) | 1.543 (0.752–3.248) |
| *P*(better) | 0.89 | 0.15 | 0.50 | 0.36 | 0.19 | 0.11 |
| ACEI+BB | | | | | | |
| Estimate (95% CrI) | 0.691 (0.448–1.037) | 1.203 (0.67–2.299) | 0.996 (0.607–1.532) | 1.102 (0.736–1.63) | 1.294 (0.917–1.87) | 1.533 (0.901–2.696) |
| *P*(better) | 0.97 | 0.26 | 0.51 | 0.28 | 0.06 | 0.05 |
| ACEI+ARB | | | | | | |
| Estimate (95% CrI) | 1 (1–1) | 1.746 (0.883–3.743) | 1.441 (0.787–2.537) | 1.594 (0.944–2.734) | 1.871 (1.111–3.326) | 2.217 (1.148–4.567) |
| *P*(better) | NA | 0.05 | 0.09 | 0.04 | 0.01 | 0.01 |
| ARB+BB | | | | | | |
| Estimate (95% CrI) | 0.573 (0.267–1.132) | 1 (1–1) | 0.824 (0.368–1.655) | 0.916 (0.427–1.838) | 1.075 (0.517–2.146) | 1.277 (0.551–2.847) |
| *P*(better) | 0.95 | NA | 0.71 | 0.60 | 0.42 | 0.26 |
| ACEI+MRA | | | | | | |
| Estimate (95% CrI) | 0.694 (0.394–1.27) | 1.213 (0.604–2.715) | 1 (1–1) | 1.106 (0.621–2.083) | 1.299 (0.755–2.439) | 1.541 (0.784–3.311) |
| *P*(better) | 0.91 | 0.29 | NA | 0.35 | 0.15 | 0.09 |
| ACEI+ARB+BB | | | | | | |
| Estimate (95% CrI) | 0.627 (0.366–1.059) | 1.092 (0.544–2.34) | 0.904 (0.48–1.61) | 1 (1–1) | 1.174 (0.702–2.045) | 1.392 (0.724–2.8) |
| *P*(better) | 0.96 | 0.40 | 0.65 | NA | 0.25 | 0.13 |
| ACEI+BB+MRA | | | | | | |
| Estimate (95% CrI) | 0.534 (0.301–0.9) | 0.93 (0.466–1.935) | 0.77 (0.41–1.325) | 0.852 (0.489–1.425) | 1 (1–1) | 1.187 (0.784–1.799) |
| *P*(better) | 0.99 | 0.58 | 0.85 | 0.75 | NA | 0.17 |
| ARNI+BB+MRA | | | | | | |
| Estimate (95% CrI) | 0.451 (0.219–0.871) | 0.783 (0.351–1.814) | 0.649 (0.302–1.275) | 0.718 (0.357–1.381) | 0.843 (0.556–1.276) | 1 (1–1) |
| *P*(better) | 0.99 | 0.74 | 0.91 | 0.87 | 0.83 | NA |

ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin-II receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; BB, beta blocker; MRA, mineralocorticoid receptor antagonist; and PLBO, placebo.

likely to be more efficacious than placebo, although with more uncertainty than the base case analysis. The sensitivity analysis showed that in comparison to placebo, ARNI was associated with a 29% reduction in mortality (HR 0.71, 95% CrI 0.39–1.17); ACEI, a 16% reduction (HR 0.84, 95% CrI 0.65–1.01); and ARB, a 12% reduction (HR 0.88, 95% CrI 0.65–1.17).

## Discussion

New trials build on the evidence from previous trials and therefore, test new drugs in addition to existing ones; as a result, it becomes increasingly difficult for clinicians to maintain a perspective on the relative efficacy of the treatments they are advised to use or to fully appreciate the cumulative benefit of combining treatments. To provide this perspective, the relative efficacy of recommended drug classes and combinations in reducing mortality of HFrEF were estimated. This is the first NMA to consider the totality of RCT evidence for recommended treatment classes and combinations, including 57 trials conducted over the past 30 years in patients with HFrEF.

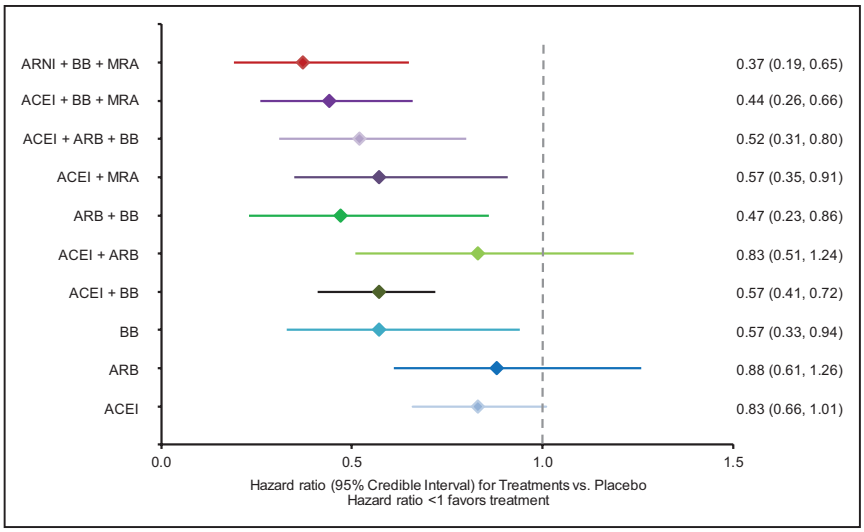


**Figure 5.** Results of random effect network meta-analysis for all-cause mortality: hazard ratios for intervention versus placebo for all-cause mortality and 95% credible intervals. ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin-II receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; BB, beta blocker; and MRA, mineralocorticoid receptor antagonist.

Our results provide insight regarding the comparative efficacy of treatments for which no head-to-head trials exist and suggest that ARNI+BB+MRA and ACEI+BB+MRA are the most efficacious treatment combinations in terms of reducing all-cause mortality. These findings validate global guidelines, which recommend first-line treatment of HFrEF with ACEI+BB (ARB+BB for those unable to tolerate ACEI), followed by the addition of an MRA as second-line therapy and ARNI to replace ACEI in patients able to tolerate ACEI (or ARB) that remain symptomatic.[5,6]

Our findings also illustrate the step-wise reductions in mortality made possible by the incremental use of combinations of disease-modifying therapies. The NMA results suggest that ARNI+BB+MRA is the most efficacious therapy, reducing all-cause mortality by 63% compared with placebo. The magnitude of this benefit represents substantial progress in terms of treatments developed over the last 30 years (since the first report of an ACEI treatment). Although this finding depends on a single trial, PARADIGM-HF was the largest trial in the network, representing 18 898 patient-years of treatment exposure.[7] It is also important to note that although BB monotherapy is included in the network and, therefore, can be compared with other monotherapies using NMA, data to support this comparison are based on 2 small, short-duration trials (CIBIS III [Cardiac Insufficiency Bisoprolol Study III][46] and CARMEN trial [Carvedilol and ACE-Inhibitor Remodelling Mild Heart Failure Evaluation][47]). The majority of available evidence regarding the efficacy of BB therapy is based on studies where patients were also receiving an ACEI (and MRA in more recent trials).

Our study is the result of a comprehensive and detailed NMA performed jointly by clinicians and methodologists. The

**Table 2. Results of Random Effect Sensitivity Analysis Network Meta-Analysis for All-Cause Mortality Rates: Difference in Intervention Versus the Comparator, 95% Credible Intervals (CrI), and Probability That the Intervention Is Better Than the Comparator [*P*(better)]**

| | Comparator | | | |
|---|---|---|---|---|
| Intervention | PLBO | ACEI | ARB | ARNI |
| PLBO | | | | |
| Estimate (95% CrI) | 1 (1–1) | 1.191 (0.995–1.537) | 1.131 (0.856–1.545) | 1.410 (0.854–2.558) |
| *P*(better) | NA | 0.03 | 0.15 | 0.06 |
| ACEI | | | | |
| Estimate (95% CrI) | 0.840 (0.651–1.005) | 1 (1–1) | 0.947 (0.699–1.234) | 1.188 (0.716–1.967) |
| *P*(better) | 0.97 | NA | 0.69 | 0.15 |
| ARB | | | | |
| Estimate (95% CrI) | 0.884 (0.647–1.169) | 1.056 (0.810–1.430) | 1 (1–1) | 1.252 (0.719–2.279) |
| *P*(better) | 0.85 | 0.31 | NA | 0.13 |
| ARNI | | | | |
| Estimate (95% CrI) | 0.709 (0.391–1.170) | 0.842 (0.508–1.396) | 0.799 (0.439–1.390) | 1 (1–1) |
| *P*(better) | 0.94 | 0.85 | 0.87 | NA |

ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin-II receptor antagonist; ARNI, angiotensin receptor-neprilysin inhibitor; and PLBO, placebo.

available data and underlying assumptions have been clearly illustrated to allow other researchers and decision-makers to critically analyze each choice and to update the analysis using a different approach. The way this study categorized the recommended drug combinations and concomitant drugs (eg, ACEIs, ARBs, BBs, and MRAs) reflects a methodological development necessary to assess the comparative efficacy of these treatment combinations. The threshold approach allowed for differences in placebo to be defined and yielded clinically meaningful results, with monotherapies being less effective than combination therapies and regimens, including 3 treatment classes likely to be most efficacious. The importance of this approach is highlighted by results of the sensitivity analysis where concomitant therapies were ignored: ARNI was associated with a 29% reduction in mortality compared with placebo, whereas the base case illustrated a 63% reduction with the combination of ARNI+BB+MRA. The difference relates to definition of placebo (as well as ACEI and ARB arms) in the sensitivity analysis, which included a wide range of concomitant drugs (eg, in CHARM-alternative trial [Candesartan in Heart Failure–Assessment of Mortality and Morbidity Alternative],[43] an ARB versus placebo trial, 55% of patients were receiving a BB), which were ignored or in some cases pooled with true placebo studies. In the base case analysis, placebo more closely represents the baseline risk of the patient population of interest because treatments were categorized based on the study drugs and concomitant drugs of interest.

Overall, findings were generally consistent with other published (network) meta-analyses evaluating all-cause mortality that compared monotherapies within a single class to placebo in addition to standard of care.[79–85] A recent putative placebo analysis by McMurray et al[86] found that ARNI was associated with a 28% reduction in all-cause mortality, which was similar to the sensitivity analysis performed that ignored background therapy (ie, 29% reduction in all-cause mortality).

Direct comparisons of results from other published studies are limited by differences in included studies and the classification of concomitant drugs, which were often ignored or led to the exclusion of several trials. Therefore, the attempt in the current study to classify trials based on the background therapies may provide more valid insight regarding treatment classes used in combination in clinical practice.

### Limitations

One limitation was the identification of concomitant therapy, which was based on data reported at baseline, which may have differed from treatments used during follow-up and certainly varied across the included trials. In addition, we assumed a class-effect, that is, all drugs in the same pharmacological class had similar efficacy, which may not be true. The same consideration applies to the dose of treatments used.

Most notably, differences were identified in terms of study duration, which may imply differences in the study purpose or type of mortality analysis. The length of follow-up in each trial was accounted for in the analysis assuming a proportional hazards model, which allowed for an assessment of the broadest evidence base. A comparison of alternative scales and statistical models may be of interest to explore alternative underlying assumptions and the consistency of direct and indirect evidence.

Despite differences identified, no inconsistencies were identified, and adjustment for patient characteristics did not have substantial impact on the results. However, it should be recognized that there is a risk of ecological bias as study-level data were used to estimate the treatment effects. Individual patient data would be required to better explore differences in treatment effect modifiers.[9,11,87] In addition, some information was not consistently reported across the trials, limiting either the assessment of potential differences or the potential to adjust for differences (ie, duration of heart failure, etiology, use of devices, or history of myocardial infarction).

To our knowledge, this review includes the broadest evidence base. However, generalizability may be limited by including only English language studies and by excluding studies enrolling patients exclusively outside of North America and Europe. Based on the available data, it was not possible to assess some comparisons, such as MRA versus placebo, as well as the combination of a BB and MRA versus placebo. Although this study provides insight regarding all-cause mortality for patients with HFrEF, other important efficacy and safety outcomes should also be considered by decision-makers, including death because of cardiovascular causes and heart failure, hospitalizations, and health-related quality of life.

### Conclusions

This report provides a comprehensive analysis of the comparative efficacy of the individual drug classes and combinations known to reduce mortality in patients with HFrEF. It was possible to pool and indirectly compare evidence from RCTs published over the last 34 years using NMA, providing insight into treatment comparisons in the absence of head-to-head trials. The threshold approach used to account for concomitant therapy provides a more accurate representation of the treatment comparisons evaluated in RCTs, often reflecting standard of care at the time. Our results show that the most efficacious combinations for reducing all-cause mortality are in line with the most recent guideline recommendations.

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## CLINICAL PERSPECTIVE

Over the past 30 years, much progress has been made regarding the treatment of patients with heart failure and reduced ejection fraction. Mortality has reduced over time, and there are now 5 main classes of life-saving pharmacological therapies recommended for the treatment of patients with heart failure and reduced ejection fraction, including angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, β-blockers, mineralocorticoid receptor antagonists, and the angiotensin receptor–neprilysin inhibitor, sacubitril/valsartan. Given that new trials build on evidence from previous trials, and the fact that new drugs have mainly been tested on top of existing ones, it becomes increasingly difficult for clinicians to maintain a perspective on the relative efficacy of the separate treatments and their combinations. This study systematically identified 57 trials conducted over the past 34 years evaluating recommended treatment classes and combinations in patients with heart failure and reduced ejection fraction. Results from the systematic review were used to estimate the relative efficacy of these therapies with regards to survival, by means of network meta-analysis, providing insight into treatment comparisons in the absence of head-to-head trials. The network meta-analysis showed that all available treatment classes and combinations were more efficacious than placebo, with the exception of angiotensin II receptor blockers monotherapy and angiotensin II receptor blockers plus angiotensin-converting enzyme inhibitors. The combination of an angiotensin receptor–neprilysin inhibitor+β-blockers+mineralocorticoid receptor antagonists resulted in the greatest mortality reduction. Overall, these findings help illustrate the step-wise reductions in mortality made possible by the incremental use of combinations of disease-modifying therapies and validate the most recent global guideline recommendations.

Circulation
Heart Failure



# Thirty Years of Evidence on the Efficacy of Drug Treatments for Chronic Heart Failure With Reduced Ejection Fraction: A Network Meta-Analysis

Heather Burnett, Amy Earley, Adriaan A. Voors, Michele Senni, John J.V. McMurray, Celine Deschaseaux and Shannon Cope

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**SUPPLEMENTAL MATERIAL**

## Expanded Methods & Results

### Search Strategy

**Databases:** Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R))

**Date of search:** April 28, 2015

1. exp Heart Failure/
2. Cardiomyopathy, Dilated/
3. (heart failure or cardiac failure or cardiac insufficiency or cardiomyopath$).tw.
4. ((cardi$ or myocard$) adj2 (failure$ or insufficien$)).tw.
5. OR/1-4
6. (LCZ696 or LCZ 696 or LCZ-696).af
7. exp dipeptidyl carboxypeptidase inhibitor/ OR exp Angiotensin-Converting Enzyme Inhibitors/
8. (angiotensin converting enzyme inhibitor OR ACEI OR ACEI OR antagonist$ OR inhibitor$ benazepril OR captopril OR enalapril OR fosinopril OR imidapril OR lisinopril OR moexipril OR perindopril OR quinapril OR ramipril OR trandolapril OR zofenopril OR alacepril OR cilazapril OR spirapril OR delapril).mp.
9. exp beta adrenergic receptor blocking agent/ OR exp Adrenergic beta-Antagonists/
10. (beta blocker$ OR BB OR acebutolol OR atenolol OR betaxolol OR bisoprolol OR carvedilol OR labetalol OR metoprolol OR nadolol OR nebivolol OR penbutolol OR pindolol OR propranolol OR sotalol OR timolol).mp.
11. exp aldosterone antagonist/

12. (aldosterone antagonist$ OR mineralocorticoid-receptor antagonist OR MRA OR eplerenone OR spironolactone).mp.
13. exp angiotensin receptor antagonist/
14. (angiotensin receptor blocker$ OR angiotensin receptor antagonist$ OR ARB OR azilsartan OR candesartan OR eprosartan OR irbesartan OR losartan OR olmesartan OR telmisartan OR valsartan).mp.
15. OR/6-14
16. "randomized controlled trial".pt.
17. (random$ or placebo$ or single blind$ or double blind$ or triple blind$).ti,ab.
18. (retraction of publication or retracted publication).pt.
19. OR/18-20
20. (animals not humans).sh.
21. ((comment or editorial or meta-analysis or practice-guideline or review or letter or journal correspondence) not "randomized controlled trial").pt.
22. (random sampl$ or random digit$ or random effect$ or random survey or random regression).ti,ab. not "randomized controlled trial".pt.
23. 20 OR 21 OR 22
24. 19 NOT 23
25. (random$ or placebo$ or single blind$ or double blind$ or triple blind$).ti,ab.
26. RETRACTED ARTICLE/
27. OR/25-26
28. (animal$ not human$).sh,hw.

29. (book or conference paper or editorial or letter or review).pt. not exp randomized controlled trial/
30. (random sampl$ or random digit$ or random effect$ or random survey or random regression).ti,ab. not exp randomized controlled trial/
31. OR/28-30
32. 27 NOT 31
33. 24 OR 32
34. 5 AND 19 AND 33
35. limit 34 to "all adult (19 plus years)" [Limit not valid in Embase; records were retained]
36. limit 35 to (adult <18 to 64 years> or aged <65+ years>) [Limit not valid in Ovid MEDLINE(R),Ovid MEDLINE(R) In-Process; records were retained]
37. limit 36 to human
38. limit 37 to yr="1987 –July 2014"

**Database:** Cochrane Library of Clinical Trials

**Date of search:** April 28, 2015

#1 MeSH descriptor: [Heart Failure] explode all trees

#2 MeSH descriptor: [Cardiomyopathy, Dilated] explode all trees

#3 (heart failure or cardiac failure or cardiac insufficiency or cardiomyopath$):ti,ab,kw (Word variations have been searched)

#4 #1 or #2 or #3

#5 (LCZ696 or LCZ 696 or LCZ-696) :ti,ab,kw

#6 MeSH descriptor: [Angiotensin-Converting Enzyme Inhibitors] explode all trees

#7 (angiotensin converting enzyme inhibitor or ACEI or ACEI or antagonist$ or inhibitor$ benazepril or captopril or enalapril or fosinopril or imidapril or lisinopril or moexipril or perindopril or quinapril or ramipril or trandolapril or zofenopril or alacepril or cilazapril or spirapril or delapril):ti,ab,kw (Word variations have been searched)

#8 MeSH descriptor: [Adrenergic beta-Antagonists] explode all trees

#9 (beta blocker$ or BB or acebutolol or atenolol or betaxolol or bisoprolol or carvedilol or labetalol or metoprolol or nadolol or nebivolol or penbutolol or pindolol or propranolol or sotalol or timolol):ti,ab,kw (Word variations have been searched)

#10 MeSH descriptor: [Mineralocorticoid Receptor Antagonists] explode all trees

#11 (aldosterone antagonist$ or mineralocorticoid-receptor antagonist or MRA or eplerenone or spironolactone):ti,ab,kw (Word variations have been searched)

#12 MeSH descriptor: [Angiotensin Receptor Antagonists] explode all trees

#13 (angiotensin receptor blocker$ or angiotensin receptor antagonist$ or ARB or azilsartan or candesartan or eprosartan or irbesartan or losartan or olmesartan or telmisartan or valsartan):ti,ab,kw (Word variations have been searched)

#14 #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13

#15 #4 and #14

#16 human not animal

#17 #15 and #16

#18 #17 in trials

#17 #18 (limit from 1987)

## Supplementary Table 1: Drug classes of interest

| Class | Generic name | Trade Name |
|---|---|---|
| ARNI | LCZ696 | Entresto |
| | valsartan/ sacubitril | |
| ACEI | benazepril | Lotensin |
| | captopril | Capoten, Lopril |
| | enalapril | Vasotec, Renitec |
| | fosinopril | Monopril |
| | imidapril | Tanatril |
| | lisinopril | Prinivil, Zestril, Tensopril, Hipril, Lisodur, Novatec |
| | moexipril | Univasc, Perdix |
| | perindopril | Aceon, Coversyl |
| | quinapril | Accupril |
| | ramipril | Altace, Tritace, Ramace, Ramiwin, Prilace, Ramipro |
| | trandolapril | Mavik |
| | zofenopril | Bifril, Teoula, Zofepril, Zopranol |
| | alacepril | Alacepul, Alaceril, Aprocorl, Asemipearl, Cenapride, Cetabavil, Cetapril, Cevozyl, Homerat, Iceden, Kananomin, Seplinok |
| | cilazapril | Cazaprol, Cilan, Cilazabace, Cilazil, Dynorm, Dynorm Plus, Inhibace Plus, Inhibace, Initiss, Inocar, Justor, Prilazid, Vascace, Zobox, Cilazapril-Teva, CO Cilazapril, Gen-Cilazapril, Inhirock, Inibace Plus, Initiss Plus, Inocar Plus |
| | spirapril | Quadropril, Renormax, Renpress, Setrilan |
| | delapril | Beniod, Delaket, Delapride, Dinapres, Trinordiol, Adecut, Araplit, Cupressin, Defolder, Virace |
| BB | acebutolol | Sectral, Prent |
| | atenolol | Tenormin, Senormin |
| | betaxolol | Kerlone, Betoptic, Lokren |
| | bisoprolol | Zebeta |
| | carvedilol | Coreg, Carvil, Dilatrend, Eucardic, Carloc |

| Class | Generic name | Trade Name |
|---|---|---|
| | labetalol | Trandate, Normodyne |
| | metoprolol | Lopressor, Toprol, Selokeen, Minax, Metrol, Betaloc, Bloxan, Neobloc, Presolol, Corvitol, Metxl, Metolar, Starpress |
| | nadolol | Corgard, Anabet, Solgol, Corzide, Alti-Nadolol, Apo-Nadol, Novo-Nadolol |
| | nebivolol | Bystolic, Nebilet, Nebilong, Nebicard, Nubeta, Nodon, Lobivon |
| | penbutolol | Levatol, Levatolol, Lobeta, Paginol, Hostabloc, Betapressin |
| | pindolol | Visken, Betapindol, Blockin L, Calvisken, Cardilate, Decreten, Durapindol, Glauco-Visken, Pectobloc, Pinbetol, Prindolol, Pynastin |
| | propranolol | Inderal, InnoPran, Avlocardyl, Deralin, Dociton, Inderalici, Sumial, Anaprilinum, Bedranol |
| | sotalol | Betapace, Sotalex, Sotacor |
| | timolol | Blocadren, Timoptic |
| MRA | eplerenone | Inspra |
| | spironolactone | Aldactone, Novo-Spiroton, Aldactazide, Spiractin, Spirotone, Verospiron, Berlactone |
| ARB | azilsartan | Edarbi |
| | candesartan | Atacand, Blopress, Amias, Ratacand |
| | eprosartan | Teveten, Eprozar |
| | irbesartan | Avapro, Karvea, Aprovel |
| | losartan | Cozaar |
| | olmesartan | Benicar, Olmetec |
| | telmisartan | Micardis, Targit, Temax, Telmore |
| | valsartan | Diovan, Angiotan, Valtan, Valzaar, Tareg |

Abbreviations: ACEI = angiotensin-converting-enzyme inhibitor; ARB = angiotensin-II receptor antagonist; ARNI = angiotensin receptor-neprilysin inhibitor; BB = beta blocker; MRA = mineralocorticoid receptor antagonist; NR = not reported; PLBO = placebo

## Supplementary Table 2: Study design and baseline patient characteristics of included RCTs

| Trial/ Author year | Study design | # centers/ location | Study duration | N | Interventions | LVEF inclusion criteria | mean LVEF (%) | % male | mean age | NYHA class 1 (%) | NYHA class 2 (%) | NYHA class 3 (%) | NYHA class 4 (%) | duration of HF (months) | Ischaemic HF (%) | Prior MI (%) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| CASSIS 1995[1] | DB, MC, PC | 18/ Czech and Slovak Rep | 104 weeks | 152<br>48<br>48 | Spirapril<br>Enalapril<br>Placebo | ≤40% | 28% | 83% | 58 | 0% | 25% | 56% | 19% | NR | 70% | 46% |
| CONSENSUS 1987[2] | DB, MC, PC | 35/ Finland, Norway, Sweden | 52 weeks | 126<br>127 | Enalapril<br>Placebo | Reduced | NR | 71% | 70 | 0% | 0% | 0% | 100% | NR | NR | 48% |
| FEST 1995[3] | DB, MC, PC | 42/ EU (8 countries) | 12 weeks | 155<br>153 | Fosinopril<br>Placebo | ≤35% | 26% | 75% | 63 | 0% | 65% | 36% | 0% | NR | 71% | NR |
| MHFT 1991[4] | DB, SC, PC | 1/ Germany | 2.7 years (median) | 83<br>87 | Captopril<br>Placebo | ≤35% | 35% | 78% | 62 | 26% | 50% | 24% | 0% | NR | 58% | 69% |
| SOLVD-prevent 1992[5] | DB, MC, PC | 23/ US, Canada, Belgium | 37.4 months (mean) | 2111<br>2117 | Enalapril<br>Placebo | ≤35% | 28% | 89% | 59 | 0% | 67% | 33% | 0% | NR | 83% | 80% |
| SOLVD-treat 1991[6] | DB, MC, PC | 23/ US, Canada, Belgium | 48 months | 1285<br>1284 | Enalapril<br>Placebo | ≤35% | 25% | 80% | 61 | 11% | 57% | 30% | 2% | NR | 71% | 66% |
| Beller 1995[7] | DB, MC, PC | 12/ US | 12 weeks | 130<br>63 | Lisinopril<br>Placebo | <45% | 28% | 75% | 60 | 0% | 35% | 56% | 9% | 36 | NR | 0% |
| Brown 1995[8] | DB, MC, PC | 41/ US | 24 weeks | 116<br>125 | Fosinopril<br>Placebo | ≤35% | 25% | 80% | 62 | 0% | 37% | 54% | 9% | NR | NR | NR |
| Chalmers 1987[9] | DB, MC, PC | 13/ 10 countries | 12 weeks | 87<br>43 | Lisinopril<br>Placebo | <45% | NR | 69% | 58 | 0% | 22% | 65% | 13% | 45 | NR | NR |
| Colfer 1992[10] | DB, MC, PC | 22/ US | 12 weeks | 114<br>58 | Benazepril<br>Placebo | ≤ 35% | 25% | 83% | 62 | 0% | 54% | 45% | 1% | 48 | 56% | NR |
| Goldstein 1988[11] | DB, SC, PC | NR/ NA | 26 weeks | 104<br>100 | Captopril<br>Placebo | ≤ 40% | 25% | 82% | 56 | 4% | 85% | 11% | 1% | 35 | 63% | NR |

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|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Lewis 1989[12] | DB, MC, PC | 13/ AUS, EU, SA, NA, Africa (10 countries) | 12 weeks | 87<br>43 | Lisinopril<br>Placebo | NR | 38% | NR | NR | 0% | 22% | 64% | 14% | 48 | NR | NR |
| Shettigar 1999[13] | DB, MC, PC | 28/ US | 12 weeks | 102<br>104 | Fosinopril<br>Placebo | ≤35% | 24% | 75% | 62 | 0% | 39% | 52% | 31% | NR | 43% | 34% |
| Veldhuisen 1999[14] | DB, MC, PC | 25/ Ntherlnds, Germany, Belgium | 12 weeks | 182<br>62 | Imidapril<br>Placebo | <45% | 34% | 77% | 61 | 0% | 77% | 23% | 0% | 35 | 63% | NR |
| SPICE 2000[15] | DB, MC, PC | 270/ NA, EU | 12 weeks | 179<br>91 | Candesartan<br>Placebo | ≤35% | 27% | 69% | 66 | 0% | 54% | 41% | 6% | NR | 71% | 62% |
| STRETCH 1999[16] | DB, MC, PC | 86/ Germany, Czech Rep, Slovenia | 12 weeks | 633<br>211 | Candesartan<br>Placebo | 30-45% | 39% | 69% | 62 | 0% | 81% | 19% | 0% | 39 | NR | NR |
| Mitrovic 2003[17] | DB, MC, PC | EU | 12 weeks | 174<br>44 | Candesartan<br>Placebo | ≤40% | 28% | 85% | 54 | 0% | 61% | 39% | 0% | 40 | NR | NR |
| ELITE I 1997[18] | DB, MC | 125/ US, SA, EU | 48 weeks | 352<br>370 | Losartan<br>Captopril | ≤40% | 30% | 67% | 73 | 0% | 65% | 34% | 2% | NR | 68% | 50% |
| ELITE II 2000[19] | DB, MC | 289/ NA, SA, EU | 700 days | 1578<br>1574 | Losartan<br>Captopril | ≤40% | 31% | 70% | 71 | 0% | 52% | 43% | 5% | NR | 79% | 58% |
| REPLACE 2001[20] | DB, MC | NR/ EU, Israel | 12 weeks | 301<br>77 | Telmisartan<br>Enalapril | <40% | 26% | 89% | 64 | 0% | 64% | 36% | 0% | NR | NR | 69% |
| Dickstein 1995[21] | DB, MC | 19/ Denmark, Finland, Norway, Sweden | 8 weeks | 108<br>58 | Losartan<br>Enalapril | ≤35% | 23% | 78% | 64 | 0% | 0% | 84% | 16% | 46 | 69% | 63% |
| Lang 1997[22] | DB, MC | 16 / NA | 12 weeks | 78<br>38 | Losartan<br>Enalapril | ≤45% | 25% | 78% | 58 | 0% | 47% | 51% | 2% | 53 | 47% | NR |
| CIBIS III 2008[23] | OL, MC | 128/ EU and AUS and Tunisia | 30 months | 505<br>505 | Bisoprolol<br>Enalapril | ≤35% | 29% | 68% | 72 | 0% | 49% | 51% | 0% | 19 | NR | 49% |

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| CARMEN 2004[24] | DB, MC, PC | 65/ EU | 18 months | 191<br>190<br>191 | Carvedilol + Placebo<br>Enalapril + Placebo<br>Carvedilol + Enalapril | <40% | 30% | 81% | 62 | 8% | 65% | 27% | 0% | NR | 67% | 52% |
| CHARM-alternative 2003[25] | DB, MC, PC | 618/ NA, EU | 3.5 years | 1013<br>1015 | Candesartan<br>Placebo | ≤40% | 30% | 68% | 67 | 0% | 48% | 49% | 4% | NR | 68% | 61% |
| HEAVEN 2002[26] | DB, MC, PC | NR/ Sweden | 12 weeks | 70<br>71 | Valsartan<br>Enalapril | ≤45% | NR | 53% | 67 | 0% | 70% | 30% | 0% | 47 | 43% | NR |
| RALES 1999[27] | DB, MC, PC | 195/ 15 countries | 24 months (mean) | 822<br>841 | Spironolactone<br>Placebo | ≤35% | 25% | 73% | 65 | 0% | 0% | 70% | 29% | NR | 54% | NR |
| Val-HeFT 2001[28] | DB, MC, PC | 302/ US, EU, Africa | 23 months (mean) | 2511<br>2499 | Valsartan<br>Placebo | <40% | 27% | 80% | 63 | 0% | 62% | 36% | 2% | NR | NR | NR |
| Hamroff 1999[29] | DB, MC | 4/ NR | 6 months | 16<br>17 | Losartan<br>Placebo | Reduced | 26% | 49% | 61 | NR | NR | NR | NR | NR | 30% | NR |
| BEST 2008[30] | DB, MC, PC | 90/ US and Canada | 3 years | 1354<br>1354 | Bucindolol<br>Placebo | ≤35% | 23% | 78% | 60 | 0% | 0% | 92% | 8% | 37 | 42% | NR |
| CIBIS I 1994[31] | DB, MC, PC | NR/ EU | 2 years | 320<br>321 | Bisoprolol<br>Placebo | < 40% | 17% | 83% | 60 | 0% | 0% | 95% | 5% | 38 | 54% | 47% |
| CIBIS II 1999[32] | DB, MC, PC | 47/ Western and Eastern EU | 1.3 years (mean) | 1327<br>1320 | Bisoprolol<br>Placebo | ≤35% | 28% | 81% | 61 | 0% | 0% | 83% | 17% | 43 | 50% | NR |
| CELICARD 2000[33] | DB, MC, PC | NR/ France, Poland | 1 year | 62<br>62 | Celiprolol<br>Placebo | <40% | 26% | 90% | 57 | 0% | 57% | 43% | 1% | NR | NR | 40% |
| COPERNICUS 2001[34] | DB, MC, PC | 334/ NA, EU, AUS | 28.7 months | 1156<br>1133 | Carvedilol<br>Placebo | <25% | 20% | 79% | 63 | 0% | NR | NR | NR | NR | 67% | NR |
| ENECA 2005[35] | DB, MC, PC | 70/ NR | 48 weeks | 134<br>126 | Nebivolol<br>Placebo | ≤35% | 26% | 73% | 72 | 0% | 49% | 47% | 5% | NR | NR | 58% |

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| MERIT-HF 1999[36] | DB, MC, PC | 14/ US, EU | 18 months | 1990<br>2001 | Metroproplol<br>Placebo | ≤40% | 28% | 78% | 64 | 0% | 41% | 55% | 4% | NR | 66% | 49% |
| MERIT-HF (pilot) 1999[37] | DB, MC, PC | NR | 6 months | 42<br>19 | Metroproplol<br>Placebo | ≤40% | 27% | 75% | NR | 0% | 56% | 41% | 3% | NR | NR | NR |
| MIC 2000[38] | DB, MC, PC | NR/ Germany, Sweden | 6 months | 26<br>26 | Metroproplol<br>Placebo | <40% | 28% | 71% | 54 | 0% | 58% | 42% | 0% | NR | NR | NR |
| MOCHA 1996[39] | DB, MC, PC | NR/ US | 6 months | 261<br>84 | Carvedilol<br>Placebo | ≤ 35% | 23% | 76% | 60 | 0% | 53% | 60% | 2% | 57 | 52% | NR |
| PRECISE 1996[40] | DB, MC, PC | 31/ US | 6 months | 133<br>145 | Carvedilol<br>Placebo | ≤35% | 22% | 73% | 60 | 0% | 40% | 56% | 4% | NR | 52% | NR |
| SYMPOXYDEX 2004[41] | DB, MC, PC | NR/ France | 6 months | 28<br>22 | Carvedilol<br>Placebo | ≤40% | 26% | 84% | 59 | 0% | 78% | 22% | 0% | NR | 40% | NR |
| Cohn 1997[42] | DB, MC, PC | 42 / US | 6 months | 70<br>35 | Carvedilol<br>Placebo | < 35% | 22% | 58% | 60 | 0% | 1% | 86% | 13% | 49 | 45% | NR |
| Colucci 1996[43] | DB, MC, PC | NR/ US | 12 months | 232<br>134 | Carvedilol<br>Placebo | ≤ 35% | 23% | 85% | 54 | 0% | 85% | 14% | 0% | 48 | 41% | NR |
| de Milliano 2002[44] | DB, MC, PC | Netherlands | 8 months | 43<br>11 | Metroproplol<br>Placebo | <35% | 25% | 67% | 65 | 0% | 54% | 46% | 0% | NR | 56% | NR |
| Dubach 2002[45] | DB, PC | NR | 1 year | 13<br>15 | Bisoprolol<br>Placebo | <40% | 26% | NR | 58 | 0% | NR | NR | 0% | NR | 57% | NR |
| Krum 1995[46] | DB, PC | NR/ US | 14 weeks | 33<br>16 | Carvedilol<br>Placebo | ≤ 35% | 16% | 78% | 55 | 0% | 27% | 63% | 10% | NR | 10% | NR |
| Packer 1996[47] | DB, MC, PC | NR/ US | 6/12 months | 696<br>398 | Carvedilol<br>Placebo | ≤ 35% | 23% | 77% | 58 | 0% | 53% | 44% | 3% | NR | NR | NR |
| Palazzuoli 2005[48] | DB, PC | Italy | 12 months | 33<br>25 | Carvedilol<br>Placebo | <40% | 32% | 66% | 71 | 0% | 0% | 57% | 43% | NR | 69% | NR |

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| Palazzuoli 2005[49] | DB, PC | Italy | 12 months | 32<br>27 | Carvedilol<br>Placebo | <40% | 32% | 64% | 71 | 0% | 0% | 58% | 42% | NR | 69% | NR |
| Sturm 2000[50] | DB, SC, PC | 1/ Austria | 2 years | 51<br>49 | Atenolol + Enalapril<br>Placebo + Enalapril | ≤25% | 17% | 88% | 52 | 0% | 78% | 20% | 2% | NR | 28% | NR |
| RESOLVD 2000[51, 52] | DB, MC, PC | 60/ NA, Italy | 43 weeks | 214<br>212 | (Candesartan, Enalapril, or Candesartan + Enalapril) + Metroprolol<br>(Candesartan, Enalapril, or Candesartan + Enalapril) + Placebo | <40% | 28% | 82% | 61 | 7% | 69% | 23% | 1% | NR | 69% | 64% |
| CHARM-added 2003[53] | DB, MC, PC | 618/ NA, EU | 3.5 years | 1276<br>1272 | Candesartan<br>Placebo | ≤40% | 28% | 79% | 64 | 0% | 24% | 73% | 0% | NR | 62% | 56% |
| AREA-IN CHF 2009[54] | DB, MC, PC | 46/ Italy | 12 months | 231<br>236 | Canrenone<br>Placebo | ≤45% | 40% | 84% | 63 | 0% | 100% | 0% | 0% | NR | 52% | NR |
| EMPHASIS-HF 2011[55] | DB, MC, PC | 278/ US, EU, AUS | 3 years | 1364<br>1373 | Eplerenone<br>Placebo | ≤30% | 26% | 78% | 69 | 0% | 100% | 0% | 0% | 58 | 69% | 50% |
| Cicoira 2002[56] | OL | Italy | 12 months | 54<br>52 | Spironolactone<br>Placebo | ≤45% | 33% | 87% | 62 | NR | NR | NR | NR | NR | 64% | NR |
| Vizzardi 2014[57] | SB, SC, PC | 1/Italy | 44 months (mean) | 65<br>65 | Spironolactone<br>Placebo | <40% | 36% | NR | 63 | 18% | 82% | 0% | 0% | NR | NR | NR |
| PARADIGM-HF 2014[58] | DB, MC | 1043/ 46 countries | 27 months (median) | 4187<br>4212 | Valsartan/ sacubitril<br>Enalapril | ≤40% | 29% | 78% | 64 | 5% | 70% | 24% | 1% | NR | 60% | 43% |

Abbreviations: AUS = Australia; d = day(s); DB = double-blind; EU = Europe; heart failure = heart failure; MC = multicentre; mos = months; MI = myocardial infarction; NA = North America; NYHA = New York heart association; LVEF = left ventricular ejection fraction; mo = month(s); NR = not reported; OL = open label; PC = placebo controlled; SB = single blind; SC = single centre; US = United States; yrs= years; wk = week(s); yr = year(s)

**Supplementary Table 3: Characteristics of included interventions and concomitant therapies reported at baseline**

| Trial/Author year | Intervention class (>50%) | Main Intervention | ACEI % | ARB % | BB % | MRA % | Digoxin % | Diuretics % |
|---|---|---|---|---|---|---|---|---|
| CASSIS 1995 | ACEI | Spirapril | 5% | NR | NR | NR | 91% | 96% |
| CASSIS 1995 | ACEI | Spirapril | 5% | NR | NR | NR | 91% | 96% |
| CASSIS 1995 | ACEI | Spirapril | 5% | NR | NR | NR | 91% | 96% |
| CASSIS 1995 | ACEI | Enalapril | 5% | NR | NR | NR | 91% | 96% |
| CASSIS 1995 | PLBO | Placebo | 5% | NR | NR | NR | 91% | 96% |
| CONSENSUS 1987 | ACEI | Enalapril | not allowed | NR | 4% | NR | 92% | 100% |
| CONSENSUS 1987 | PLBO | Placebo | not allowed | NR | 2% | NR | 94% | 100% |
| FEST 1995 | ACEI | Fosinopril | NR | NR | NR | NR | 61% | 100% |
| FEST 1995 | PLBO | Placebo | NR | NR | NR | NR | 62% | 100% |
| MHFT 1991 | ACEI | Captopril | NR | NR | 23% | NR | 59% | 79% |
| MHFT 1991 | PLBO | Placebo | NR | NR | 23% | NR | 59% | 79% |
| SOLVD-prevent 1992 | ACEI | Enalapril | not allowed | NR | NR | NR | 12% | 16% |
| SOLVD-prevent 1992 | PLBO | Placebo | not allowed | NR | NR | NR | 13% | 17% |
| SOLVD-treat 1991 | ACEI | Enalapril | not allowed | NR | 8% | NR | 66% | 86% |
| SOLVD-treat 1991 | PLBO | Placebo | not allowed | NR | 7% | NR | 68% | 85% |
| Beller 1995 | ACEI | Lisinopril | NR | NR | NR | NR | 94% | 99% |
| Beller 1995 | PLBO | Placebo | NR | NR | NR | NR | 86% | 97% |
| Brown 1995 | ACEI | Fosinopril | not allowed | NR | not allowed | NR | 53% | 100% |
| Brown 1995 | PLBO | Placebo | not allowed | NR | not allowed | NR | 54% | 100% |
| Chalmers 1987 | ACEI | Lisinopril | NR | NR | NR | 10% | 60% | 55% |
| Chalmers 1987 | PLBO | Placebo | NR | NR | NR | 14% | 72% | 49% |
| Colfer 1992 | ACEI | Benazepril | NR | NR | not allowed | NR | 100% | 100% |
| Colfer 1992 | PLBO | Placebo | NR | NR | not allowed | NR | 100% | 100% |
| Goldstein 1988 | ACEI | Captopril | NR | NR | NR | NR | 60% | NR |
| Goldstein 1988 | PLBO | Placebo | NR | NR | NR | NR | 67% | NR |
| Lewis 1989 | ACEI | Lisinopril | NR | NR | NR | NR | 100% | 100% |
| Lewis 1989 | PLBO | Placebo | NR | NR | NR | NR | 100% | 100% |

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|---|---|---|---|---|---|---|---|---|
| Shettigar 1999 | ACEI | Fosinopril | not allowed | NR | not allowed | NR | 42% | 100% |
| Shettigar 1999 | PLBO | Placebo | not allowed | NR | not allowed | NR | 47%% | 100% |
| Veldhuisen 1999 | ACEI | Imidapril | NR | NR | not allowed | NR | 23% | 34% |
| Veldhuisen 1999 | ACEI | Imidapril | NR | NR | not allowed | NR | 26% | 25% |
| Veldhuisen 1999 | ACEI | Imidapril | NR | NR | not allowed | NR | 24% | 30% |
| Veldhuisen 1999 | PLBO | Placebo | NR | NR | not allowed | NR | 19% | 25% |
| SPICE 2000 | ARB | Candesartan | not allowed | not allowed | 22% | NR | 60% | NR |
| SPICE 2000 | PLBO | Placebo | not allowed | not allowed | 20% | NR | 63% | NR |
| STRETCH 1999 | ARB | Candesartan | not allowed | NR | 1% | NR | 40% | 61% |
| STRETCH 1999 | ARB | Candesartan | not allowed | NR | 1% | NR | 43% | 63% |
| STRETCH 1999 | ARB | Candesartan | not allowed | NR | 0% | NR | 42% | 58% |
| STRETCH 1999 | PLBO | Placebo | not allowed | NR | 1% | NR | 39% | 58% |
| Mitrovic 2003 | ARB | Candesartan | not allowed | not allowed | NR | NR | 78% | NR |
| Mitrovic 2003 | ARB | Candesartan | not allowed | not allowed | NR | NR | 65% | NR |
| Mitrovic 2003 | ARB | Candesartan | not allowed | not allowed | NR | NR | 80% | NR |
| Mitrovic 2003 | ARB | Candesartan | not allowed | not allowed | NR | NR | 77% | NR |
| Mitrovic 2003 | PLBO | Placebo | not allowed | not allowed | NR | NR | 82% | NR |
| ELITE I 1997 | ARB | Losartan | not allowed | not allowed | 16% | NR | 57% | 74% |
| ELITE I 1997 | ACEI | Captopril | not allowed | not allowed | 17% | NR | 56% | 74% |
| ELITE II 2000 | ARB | Losartan | not allowed | not allowed | 23% | NR | 50% | 77% |
| ELITE II 2000 | ACEI | Captopril | not allowed | not allowed | 21% | NR | 50% | 79% |
| REPLACE 2001 | ACEI | Enalapril | not allowed | not allowed | NR | NR | 39% | NR |
| REPLACE 2001 | ARB | Telmisartan | not allowed | not allowed | NR | NR | 39% | NR |
| REPLACE 2001 | ARB | Telmisartan | not allowed | not allowed | NR | NR | 39% | NR |
| REPLACE 2001 | ARB | Telmisartan | not allowed | not allowed | NR | NR | 39% | NR |
| REPLACE 2001 | ARB | Telmisartan | not allowed | not allowed | NR | NR | 39% | NR |
| Dickstein 1995 | ARB | Losartan | NR | NR | 19% | NR | 58% | NR |
| Dickstein 1995 | ARB | Losartan | NR | NR | 11% | NR | 73% | NR |
| Dickstein 1995 | ACEI | Enalapril | NR | NR | 7% | NR | 59% | NR |
| Lang 1997 | ARB | Losartan | not allowed | NR | 11% | NR | 82% | 100% |
| Lang 1997 | ARB | Losartan | not allowed | NR | 3% | NR | 85% | 100% |
| Lang 1997 | ACEI | Enalapril | not allowed | NR | 8% | NR | 87% | 97% |

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|---|---|---|---|---|---|---|---|---|
| CIBIS III 2008 | BB | Bisoprolol then Enalapril | not allowed | NR | not allowed | 14% | 33% | NR |
| CIBIS III 2008 | ACEI | Enalapril then Bisoprolol | not allowed | NR | not allowed | 12% | 31% | NR |
| CARMEN 2004 | BB | Carvedilol + placebo | not allowed | NR | not allowed | 15% | 44% | 67% |
| CARMEN 2004 | ACEI | Enalapril + placebo | not allowed | NR | not allowed | 13% | 44% | 74% |
| CARMEN 2004 | ACEI + BB | Carvedilol + enalapril | not allowed | NR | not allowed | 12% | 47% | 73% |
| RALES 1999 | ACEI + MRA | Spironolactone | 95% | NR | 11% | not allowed | 75% | 95% |
| RALES 1999 | ACEI | Placebo | 94% | NR | 10% | not allowed | 72% | 94% |
| Val-HeFT 2001 | ACEI + ARB | Valsartan | 93% | not allowed | 35% | NR | 67% | NR |
| Val-HeFT 2001 | ACEI | Placebo | 93% | not allowed | 35% | NR | 68% | NR |
| Hamroff 1999 | ACEI + ARB | Losartan | 100% | NR | 6% | NR | 100% | 100% |
| Hamroff 1999 | ACEI | Placebo | 100% | NR | 6% | NR | 94% | 100% |
| BEST 2001 | ACEI + BB | Bucindolol | 91% | 6% | not allowed | 3% | 93% | NR |
| BEST 2001 | ACEI | Placebo | 91% | 7% | not allowed | 4% | 92% | NR |
| CELICARD 2000 | ACEI + BB | Celiprolol | 80% | NR | not allowed | NR | 51% | NR |
| CELICARD 2000 | ACEI | Placebo | 90% | NR | not allowed | NR | 66% | NR |
| CIBIS I 1994 | ACEI + BB | Bisoprolol | 89% | NR | NR | NR | 57% | 100% |
| CIBIS I 1994 | ACEI | Placebo | 91% | NR | NR | NR | 56% | 100% |
| CIBIS II 1999 | ACEI + BB | Bisoprolol | 96% | NR | NR | NR | 53% | 98% |
| CIBIS II 1999 | ACEI | Placebo | 96% | NR | NR | NR | 51% | 99% |
| COPERNICUS 2001 | ACEI + BB | Carvedilol | 97%* | 97%* | not allowed | 19% | 67% | NR |
| COPERNICUS 2001 | ACEI | Placebo | 97%* | 97%* | not allowed | 20% | 65% | NR |
| ENECA 2005 | ACEI + BB | Nebivolol | 91% | 5% | not allowed | NR | 60% | NR |
| ENECA 2005 | ACEI | Placebo | 92% | 7% | not allowed | NR | 53% | NR |
| MERIT-heart failure 1999 | ACEI + BB | Metoprolol | 89% | 7% | not allowed | 7% | 63% | 91% |
| MERIT-heart failure 1999 | ACEI | Placebo | 90% | 6% | not allowed | 8% | 64% | 90% |
| MERIT-heart failure (pilot) 1999 | ACEI + BB | Metoprolol | 95% | NR | NR | NR | 91% | NR |
| MERIT-heart failure (pilot) 1999 | ACEI | Placebo | 89% | NR | NR | NR | 90% | NR |
| MIC 2000 | ACEI + BB | Metoprolol | 92% | NR | not allowed | NR | 51% | NR |
| MIC 2000 | ACEI | Placebo | 91% | NR | not allowed | NR | 52% | NR |
| MOCHA 1996 | ACEI + BB | Carvedilol (low-dose) | 93% | NR | not allowed | NR | 99% | 98% |
| MOCHA 1996 | ACEI + BB | Carvedilol (medium-dose) | 99% | NR | not allowed | NR | 88% | 96% |

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|---|---|---|---|---|---|---|---|---|
| MOCHA 1996 | ACEI + BB | Carvedilol (high-dose) | 89% | NR | not allowed | NR | 90% | 93% |
| MOCHA 1996 | ACEI | Placebo | 94% | NR | not allowed | NR | 93% | 93% |
| PRECISE 1996 | ACEI + BB | Carvedilol | 96% | NR | not allowed | NR | 91% | 98% |
| PRECISE 1996 | ACEI | Placebo | 97% | NR | not allowed | NR | 88% | 99% |
| SYMPOXYDEX 2004 | ACEI + BB | Carvedilol | 96% | NR | not allowed | NR | NR | 100% |
| SYMPOXYDEX 2004 | ACEI | Placebo | 96% | NR | not allowed | NR | NR | 100% |
| Cohn 1997 | ACEI + BB | Carvedilol | 94% | NR | NR | NR | 90% | 97% |
| Cohn 1997 | ACEI | Placebo | 91% | NR | NR | NR | 89% | 100% |
| Colucci 1996 | ACEI + BB | Carvedilol | 98% | NR | not allowed | NR | 89% | NR |
| Colucci 1996 | ACEI | Placebo | 98% | NR | not allowed | NR | 89% | NR |
| de Milliano 2002 | ACEI + BB | Metoprolol | 93% | NR | not allowed | NR | 28% | NR |
| de Milliano 2002 | ACEI | Placebo | 91% | NR | not allowed | NR | 36% | NR |
| Dubach 2002 | ACEI + BB | Bisoprolol | 100% | NR | not allowed | NR | 5% | NR |
| Dubach 2002 | ACEI | Placebo | 100% | NR | not allowed | NR | 9% | NR |
| Krum 1995 | ACEI + BB | Carvedilol | 90% | NR | NR | NR | NR | NR |
| Krum 1995 | ACEI | Placebo | 90% | NR | NR | NR | NR | NR |
| Packer 1996 | ACEI + BB | Carvedilol | 95% | NR | not allowed | NR | 91% | 95% |
| Packer 1996 | ACEI | Placebo | 95% | NR | not allowed | NR | 90% | 95% |
| Palazzuoli 2005 | ACEI + BB | Carvedilol | 100% | NR | not allowed | NR | NR | NR |
| Palazzuoli 2005 | ACEI | Placebo | 100% | NR | not allowed | NR | NR | NR |
| Palazzuoli 2005 | ACEI + BB | Carvedilol | 100% | NR | not allowed | NR | NR | NR |
| Palazzuoli 2005 | ACEI | Placebo | 100% | NR | not allowed | NR | NR | NR |
| Sturm 2000 | ACEI + BB | Atenolol + enalapril | 100% | NR | not allowed | NR | 51% | NR |
| Sturm 2000 | ACEI | Placebo + enalapril | 100% | NR | not allowed | NR | 49% | NR |
| HEAVEN 2002 | ARB + BB | Valsartan | not allowed | not allowed | 52% | NR | 26% | NR |
| HEAVEN 2002 | ACEI + BB | Enalapril | not allowed | not allowed | 56% | NR | 32% | NR |
| CHARM-alternative 2003 | ARB + BB | Candesartan | not allowed | not allowed | 55% | 25% | 60% | NR |
| CHARM-alternative 2003 | BB | Placebo | not allowed | not allowed | 55% | 23% | 63% | NR |
| RESOLVD 2000 | ACEI + ARB + BB | (Candesartan, enalapril, or candesartan + enalapril) + metoprolol | ACEI alone: 14%<br>ACEI + ARB: 41% | ARB alone: 45% | not allowed | NR | 65% | NR |
| RESOLVD 2000 | ACEI + ARB | (Candesartan, enalapril, or candesartan + enalapril) + placebo | ACEI alone: 19% | ARB alone: 40% | not allowed | NR | 69% | NR |

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|---|---|---|---|---|---|---|---|---|
| RESOLVD 2003 | ARB + BB | (Candesartan or enalapril) + metoprolol | ACEI + ARB: 41% 23% | 77% | not allowed | NR | 68% | 82% |
| RESOLVD 2003 | ACEI + ARB + BB | (Candesartan + enalapril) + metoprolol | not allowed | not allowed | not allowed | NR | 62% | 83% |
| RESOLVD 2003 | ARB | (Candesartan or enalapril) + placebo | 33% | 67% | not allowed | NR | 74% | 85% |
| RESOLVD 2003 | ACEI + ARB | (Candesartan + enalapril) + placebo | not allowed | not allowed | not allowed | NR | 70% | 83% |
| CHARM-added 2003 | ACEI + ARB + BB | Candesartan | 100% | not allowed | 55% | 17% | 58% | NR |
| CHARM-added 2003 | ACEI + BB | Placebo | 100% | not allowed | 56% | 17% | 59% | NR |
| AREA-IN CHF 2009 | ACEI + BB + MRA | Canrenone | 85% | 12% | 81% | not allowed | 24% | NR |
| AREA-IN CHF 2009 | ACEI + BB | Placebo | 75% | 24% | 78% | not allowed | 27% | NR |
| EMPHASIS-heart failure 2011 | ACEI + BB + MRA | Eplerenone | 78% | 19% | 87% | not allowed | 27% | 84% |
| EMPHASIS-heart failure 2011 | ACEI + BB | Placebo | 77% | 19% | 87% | not allowed | 28% | 86% |
| Cicoira 2002 | ACEI + BB + MRA | Spironolactone | 100% | NR | 72% | not allowed | NR | NR |
| Cicoira 2002 | ACEI + BB | Placebo | 100% | NR | 65% | not allowed | NR | NR |
| Vizzardi 2014 | ACEI + BB + MRA | Spironolactone | 100%* | 100%* | 97% | NR | NR | 75% |
| Vizzardi 2014 | ACEI + BB | Placebo | 100%* | 100%* | 98% | NR | NR | 86% |
| PARADIGM-heart failure 2014 | ARNI + BB + MRA | Sacubitril/valsartan | not allowed | NR | 93% | 54% | 29% | 80% |
| PARADIGM-heart failure 2014 | ACEI + BB + MRA | Enalapril | not allowed | NR | 93% | 57% | 31% | 80% |

* data presented for ACEI/ARB

Abbreviations: ACEI = angiotensin-converting-enzyme inhibitor; ARB = angiotensin-II receptor antagonist; ARNI = angiotensin receptor-neprilysin inhibitor; BB = beta blocker; MRA = mineralocorticoid receptor antagonist; NR = not reported; PLBO = placebo

**Supplementary Table 4: Proportion of patients taking concomitant ACEI and ARB in RCTs that allow concomitant use of ACEI or ARB**

| Criteria for ACEI or ARB | n studies | % of studies |
|---|---|---|
| ACEI or ARB allowed | 9 | 100% |
| ≥90% patients taking ACEI | 3/9 | 33% |
| ≥75% patients taking ACEI | 6/9 | 67% |
| Only present pooled % (ACEI or ARB) | 2/9 | 22% |
| Treatment classification unclear* | 1/9 | 11% |

***** RESOLVD trial [51,52]

Abbreviations: ACEI = angiotensin-converting-enzyme inhibitor; ARB = angiotensin-II receptor antagonist

## Supplementary Table 5: Treatment doses and schedules by molecule

| Intervention class (>50%) | Trial/Author year | Main Intervention | Target dosage | Frequency | Target daily dosage | Treatment duration |
|---|---|---|---|---|---|---|
| ACEI | Colfer 1992 | Benazepril | 20mg | OD | 20mg | 12 weeks (titration first 8 weeks) |
| ACEI | MHFT 1991 | Captopril | 25mg | BID | 40mg | Median: 2.7 years |
| ACEI | ELITE I 1997 | Captopril | 50mg | TID | 150mg | 48 weeks (uptitration every 7 days) |
| ACEI | ELITE II 2000 | Captopril | 50mg | TID | 150mg | 700 days |
| ACEI | Anonymous 1988 | Captopril | 50mg | TID | 150mg | 24 weeks (uptitrated from 25mg/day if tolerated) |
| ACEI | Dickstein 1995 | Enalapril | 10mg | BID | 20mg | 8 weeks |
| ACEI | REPLACE 2001 | Enalapril | 10mg | BID | 20mg | 12 weeks |
| ACEI | CARMEN 2004 | Enalapril | 10mg | BID | 20mg | 18 months (plus upward titration and downward titration, undefined lengths of time |
| ACEI | CASSIS 1995 | Enalapril | 10mg | OD | 10mg | 12 weeks |
| ACEI | SOLVD-treat 1991 | Enalapril | 10mg | BID | 20mg | 48 months |
| ACEI | SOLVD-prevent 1992 | Enalapril | 10mg | BID | 20mg | 37.4 months (mean) |
| ACEI | CIBIS III 2008 | Enalapril | 10mg | BID | 20mg/10mg | 6 months |
| ACEI | CONSENSUS 1987 | Enalapril | 10mg-20mg | BID | 20mg-40mg | 52 weeks |
| ACEI | Lang 1997 | Enalapril | 20mg | BID | 40mg | 12 weeks |
| ACEI | Sturm 2000 | Enalapril | 40mg | OD | 40mg | 2 years (includes titration) |
| ACEI | Brown 1995 | Fosinopril | 20mg | OD | 20mg | 24 weeks |
| ACEI | FEST 1995 | Fosinopril | 40mg | OD | 40mg | 12 weeks |
| ACEI | Shettigar 1999 | Fosinopril | 40mg | OD | 40mg | 12 weeks (uptitration over first 4-weeks) |
| ACEI | Veldhuisen 1999* | Imidapril | 2.5mg | OD | 2.5mg | 12 weeks |
| ACEI | Veldhuisen 1999* | Imidapril | 5mg | OD | 5mg | 12 weeks |
| ACEI | Veldhuisen 1999 | Imidapril | 10mg | OD | 10mg | 12 weeks |
| ACEI | Beller 1995 | Lisinopril | 5mg-20mg | OD | 5mg-20mg | 12 weeks |
| ACEI | Chalmers 1987 | Lisinopril | 5mg-20mg | OD | 5mg-20mg | 12 weeks |

| | | | | | | |
|---|---|---|---|---|---|---|
| ACEI | Lewis 1989 | Lisinopril | 5-20mg | OD | 5-20mg | 12 weeks |
| ACEI | CASSIS 1995* | Spirapril | 1.5mg | OD | 1.5mg | 12 weeks |
| ACEI | CASSIS 1995* | Spirapril | 3mg | OD | 3mg | 12 weeks |
| ACEI | CASSIS 1995 | Spirapril | 6mg | OD | 6mg | 12 weeks |
| ACEI | MERIT-heart failure 1999 | Placebo | NA | NA | NA | 18 months (including 6-8 week titration) |
| ACEI | MOCHA 1996 | Placebo | NA | NA | NA | 6 months (plus 2-4 week titration) |
| ACEI | SYMPOXYDEX 2004 | Placebo | NA | NA | NA | 6 months (including 6 weeks titration) |
| ACEI | Cohn 1997 | Placebo | NA | NA | NA | 6 months (plus 4 week titration) |
| ACEI | Val-HeFT 2001 | Placebo | NA | NA | NA | 38 months (including 4 weeks titration) |
| ACEI | de Milliano 2002 | Placebo | NA | NA | NA | 6 months (plus 10 wks titration) |
| ACEI | Dubach 2002 | Placebo | NA | NA | NA | 12 months (titration first month) |
| ACEI | ENECA 2005 | Placebo | NA | NA | NA | 48 weeks (includes 6 week titration period) |
| ACEI | BEST 2001 | Placebo | NA | NA | NA | 42 months (titration first 6 weeks) |
| ACEI | MIC 2000 | Placebo | NA | NA | NA | 6 months (including 6 week titration) |
| ACEI | MERIT-heart failure (pilot) 1999 | Placebo | NA | NA | NA | 26 weeks (titration first 8 weeks) |
| ACEI | Hamroff 1999 | Placebo | NA | NA | NA | 6 months |
| ACEI | CIBIS I 1994 | Placebo | NA | NA | NA | 2 years (mean duration 1.9) |
| ACEI | CIBIS II 1999 | Placebo | NA | NA | NA | mean duration: 1.3 years (titration weeks 1-5) |
| ACEI | PRECISE 1996 | Placebo | NA | NA | NA | 6 months |
| ACEI | Packer 1996 | Placebo | NA | NA | NA | 6 months (plus 2-10 week titration (mild heart failure protocol;12 months + titration) |
| ACEI | Colucci 1996 | Placebo | NA | NA | NA | 52 weeks (plus uptitration 2-6 weeks) |
| ACEI | Krum 1995 | Placebo | NA | NA | NA | 14 weeks (titration in first week) |
| ACEI | COPERNICUS 2001 | Placebo | NA | NA | NA | 28.7 months (includes approximately 8 week titration period) |
| ACEI | Palazzuoli 2005 | Placebo | NA | NA | NA | 12 months (titration first 7 weeks) |
| ACEI | Palazzuoli 2005 | Placebo | NA | NA | NA | 12 months (titration first 7 weeks) |
| ACEI | RALES 1999 | Placebo | NA | NA | NA | 24 months |

| | | | | | | |
|---|---|---|---|---|---|---|
| ACEI | CELICARD 2000 | Placebo | NA | NA | NA | 1 year (including 1 month titration period) |
| BB | CIBIS III 2008 | Bisoprolol | 10mg | OD | 10mg | 26 weeks (including 10 week titration) |
| BB | CARMEN 2004 | Carvedilol | 25mg or 50mg if >85kg | BID | 50mg or 100mg if >85kg | 18 months (plus upward titration and downward titration, undefined lengths of time |
| BB | CHARM-alternative 2003 | Placebo | NA | NA | NA | 33.7 months (median follow-up, plus 6 weeks titration period) |
| ARB | SPICE 2000 | Candesartan | 16mg | OD | 16mg | 12 weeks (including 4 weeks titration) |
| ARB | STRETCH1999* | Candesartan | 4mg | OD | 4mg | 12 weeks |
| ARB | STRETCH1999* | Candesartan | 8mg | OD | 8mg | 12 weeks |
| ARB | STRETCH1999 | Candesartan | 16mg | OD | 16mg | 12 weeks |
| ARB | Lang 1997 | Losartan* | 25mg | OD | 25mg | 12 weeks |
| ARB | Lang 1997 | Losartan | 50mg | OD | 50mg | 12 weeks |
| ARB | Mitrovic 2003* | Candesartan | 2mg | OD | 2mg | 12 weeks (titration first 3 weeks) |
| ARB | Mitrovic 2003* | Candesartan | 4mg | OD | 4mg | 12 weeks (titration first 3 weeks) |
| ARB | Mitrovic 2003* | Candesartan | 8mg | OD | 8mg | 12 weeks (titration first 3 weeks) |
| ARB | Mitrovic 2003 | Candesartan | 16mg | OD | 16mg | 12 weeks (titration first 3 weeks) |
| ARB | Dickstein 1995* | Losartan | 25mg | OD | 25mg | 8 weeks |
| ARB | Dickstein 1995 | Losartan | 50mg | OD | 50mg | 8 weeks |
| ARB | ELITE I 1997 | Losartan | 50mg | OD | 50mg | 48 weeks (uptitration every 7 days) |
| ARB | ELITE II 2000 | Losartan | 50mg | OD | 50mg | 700 days |
| ARB | REPLACE 2001* | Telmisartan | 10mg | OD | 10mg | 12 weeks |
| ARB | REPLACE 2001* | Telmisartan | 20mg | OD | 20mg | 12 weeks |
| ARB | REPLACE 2001* | Telmisartan | 40mg | OD | 40mg | 12 weeks |
| ARB | REPLACE 2001 | Telmisartan | 80mg | OD | 80mg | 12 weeks |
| ACEI + ARB | RESOLVD 2003 | (Candesartan + enalapril) + placebo | NA | NA | NA | 19 weeks without placebo (including mean titration 93 days), placebo received for 24weeks (43 weeks total) |
| ACEI + ARB | Hamroff 1999 | Losartan | 50mg | OD | 50mg | 6 months |
| ACEI + ARB | Val-HeFT 2001 | Valsartan | 160mg | BID | 320mg | 38 months (including 4 weeks titration) |

| | | | | | | |
|---|---|---|---|---|---|---|
| ACEI + BB | Sturm 2000 | Atenolol + enalapril | 50mg-100mg/40mg | daily | 50mg-100mg/40mg | 2 years (includes titration) |
| ACEI + BB | Dubach 2002 | Bisoprolol | 10mg | daily | 10mg | 12 months (titration first month) |
| ACEI + BB | CIBIS I 1994 | Bisoprolol | 5mg | OD | 5mg | 2 years (mean duration 1.9) |
| ACEI + BB | CIBIS II 1999 | Bisoprolol | 2.5-10mg | OD | 2.5-10mg | mean duration: 1.3 years (titration weeks 1-5) |
| ACEI + BB | BEST 2001 | Bucindolol | 50mg if <75kg; 100mg if >75kg | BID | 100mg or 200mg | 42 months (titration first 6 weeks) |
| ACEI + BB | SYMPOXYDEX 2004 | Carvedilol | 25mg | BID | 50mg | 6 months (including 6 weeks titration) |
| ACEI + BB | Cohn 1997 | Carvedilol | 25mg | BID | 50mg | 6 months (plus 4 week titration) |
| ACEI + BB | PRECISE 1996 | Carvedilol | 25mg | BID | 50mg | 6 months |
| ACEI + BB | Krum 1995 | Carvedilol | 25mg | BID | 50mg | 14 weeks (titration in first week) |
| ACEI + BB | Packer 1996 | Carvedilol | 25-50mg | BID | 50mg-100mg | 6 months (plus 2-10 week titration (mild heart failure protocol;12 months + titration) |
| ACEI + BB | Colucci 1996 | Carvedilol | 25-50mg | BID | 50-100mg | 52 weeks (plus uptitration 2-6 weeks) |
| ACEI + BB | COPERNICUS 2001 | Carvedilol | 25mg | BID | 50mg | 28.7 months (includes approximately 8 week titration period) |
| ACEI + BB | Palazzuoli 2005 | Carvedilol | 50mg | daily | 50mg | 12 months (titration first 7 weeks) |
| ACEI + BB | Palazzuoli 2005 | Carvedilol | 50mg | daily | 50mg | 12 months (titration first 7 weeks) |
| ACEI + BB | MOCHA 1996* | Carvedilol (low-dose) | 6.25mg | BID | 12.5mg | 6 months (plus 2-4 week titration) |
| ACEI + BB | MOCHA 1996* | Carvedilol (medium-dose) | 12.5mg | BID | 25mg | 6 months (plus 2-4 week titration) |
| ACEI + BB | MOCHA 1996 | Carvedilol (high-dose) | 25mg | BID | 50mg | 6 months (plus 2-4 week titration) |
| ACEI + BB | CARMEN 2004 | Carvedilol + enalapril | 25mg or 50mg if >85kg/10mg | BID | 50mg or 100mg if >85kg/20mg | 18 months (plus upward titration and downward titration, undefined lengths of time |
| ACEI + BB | CELICARD 2000 | Celiprolol | 100mg | OD | 100mg | 1 year (including 1 month titration period) |

| | | | | | | |
|---|---|---|---|---|---|---|
| ACEI + BB | MERIT-heart failure 1999 | Metoprolol | 200mg | daily | 200mg | 18 months (including 6-8 week titration) |
| ACEI + BB | MERIT-heart failure (pilot) 1999 | Metoprolol | 150mg | o.d. | 150 mg | 26 weeks (titration first 8 weeks) |
| ACEI + BB | de Milliano 2002 | Metoprolol | 50, 100 or 150mg | daily | 50, 100 or 150mg | 6 months (plus 10 wks titration) |
| ACEI + BB | MIC 2000 | Metoprolol | NR | NR | 135mg (mean) | 6 months (including 6 week titration) |
| ACEI + BB | ENECA 2005 | Nebivolol | 10mg | daily | 10mg | 48 weeks (includes 6 week titration period) |
| ACEI + BB | HEAVEN 2002 | Enalapril | 10mg | BID | 20mg | 12 weeks (including titration) |
| ACEI + BB | AREA-IN CHF 2009 | Placebo | NA | NA | NA | 12 months |
| ACEI + BB | Cicoira 2002 | Placebo | NA | NA | NA | 12 months (includes titration) |
| ACEI + BB | Vizzardi 2014 | Placebo | 25mg | OD | 25mg | 44 months (mean) |
| ACEI + BB | CHARM-added 2003 | Placebo | NA | NA | NA | 41 months (median follow-up, plus 6 weeks titration period) |
| ACEI + BB | EMPHASIS-heart failure 2011 | Placebo | NA | NA | NA | 3 years |
| ARB + BB | HEAVEN 2002 | Valsartan | 160mg | OD | 160mg | 12 weeks (including titration) |
| ARB + BB | CHARM-alternative 2003 | Candesartan | 32mg | OD | 32mg | 33.7 months (median follow-up, plus 6 weeks titration period) |
| ACEI + MRA | RALES 1999 | Spironolactone | 25-50mg | OD | 25-50mg (mean 30mg) | 24 months |
| ACEI + ARB + BB | RESOLVD 2003 | (Candesartan + enalapril) + metoprolol | 200mg | daily | 200mg | 19 weeks without metoprolol (including mean titration 93 days), metoprolol received for 24weeks (43 weeks total) |
| ACEI + ARB + BB | CHARM-added 2003 | Candesartan | 32mg | OD | 32mg | 41 months (median follow-up, plus 6 weeks titration period) |
| ACEI + BB + MRA | AREA-IN CHF 2009 | Canrenone | 50mg | OD | 50mg | 12 months |
| ACEI + BB + MRA | EMPHASIS-heart failure 2011 | Eplerenone | 50mg | OD | 50mg | 3 years |
| ACEI + BB + MRA | PARADIGM-heart failure 2014 | Enalapril | 10mg | BID | 20mg | 27 months (median) |
| ACEI + BB + MRA | Cicoira 2002 | Spironolactone | 50mg | OD | 50mg | 12 months (includes titration) |

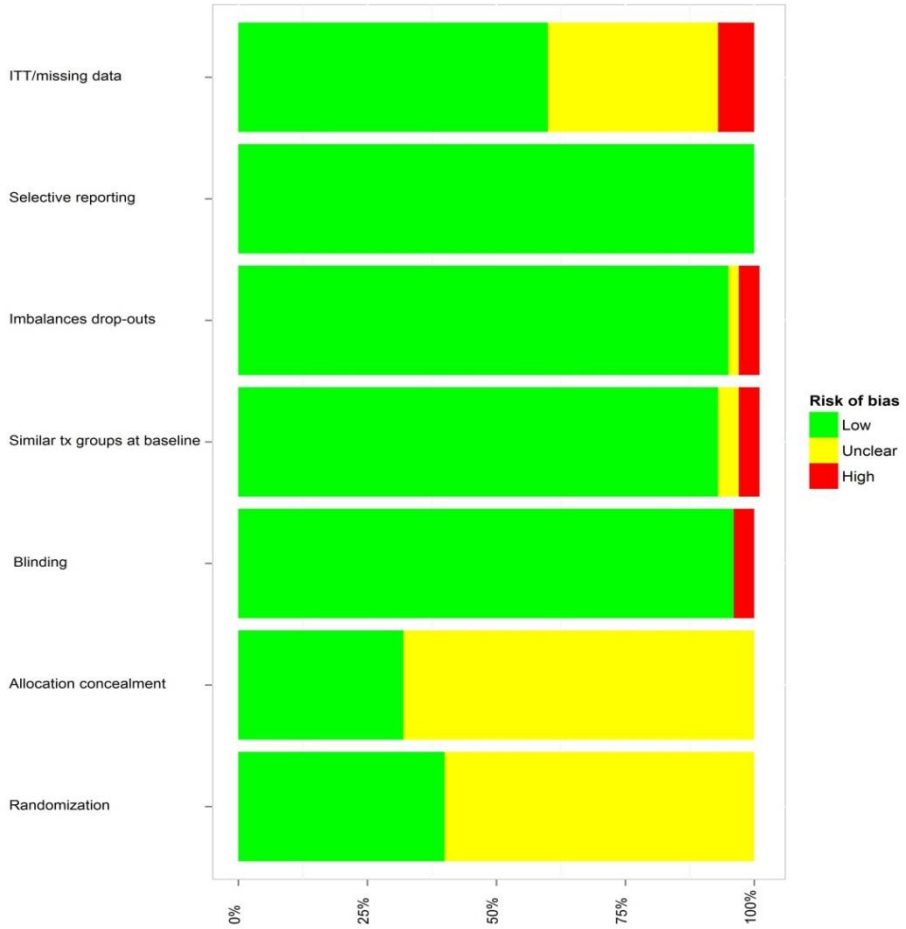
| | | | | | | |
|---|---|---|---|---|---|---|
| ACEI + BB + MRA | Vizzardi 2014 | Spironolactone | 25mg-100mg | OD-QID | 25mg-400mg | 44 months (mean) |
| ARNI + BB + MRA | PARADIGM-heart failure 2014 | Sacubitril/valsartan | 200mg | BID | 400mg | 27 months (median) |
| PLBO | Beller 1995 | Placebo | 5mg-20mg | OD | 5mg-20mg | 12 weeks |
| PLBO | Brown 1995 | Placebo | NA | NA | NA | 24 weeks |
| PLBO | Chalmers 1987 | Placebo | 5mg-20mg | OD | 5mg-20mg | 12 weeks |
| PLBO | STRETCH 1999 | Placebo | NA | NA | NA | 12 weeks |
| PLBO | Anonymous 1988 | Placebo | NA | NA | NA | 24 weeks (uptitrated from 25mg/day if tolerated) |
| PLBO | Colfer 1992 | Placebo | NA | NA | NA | 12 weeks (titration first 8 weeks) |
| PLBO | FEST 1995 | Placebo | NA | NA | NA | 12 weeks |
| PLBO | SPICE 2000 | Placebo | NA | NA | NA | 12 weeks (including 4 weeks titration) |
| PLBO | MHFT 1991 | Placebo | NA | NA | NA | Median: 2.7 years |
| PLBO | Lewis 1989 | Placebo | NA | NA | NA | 12 weeks |
| PLBO | Mitrovic 2003 | Placebo | NA | NA | NA | 12 weeks (titration first 3 weeks) |
| PLBO | Shettigar 1999 | Placebo | NA | NA | NA | 12 weeks (uptitration over first 4-weeks) |
| PLBO | CONSENSUS 1987 | Placebo | NA | NA | NA | 52 weeks |
| PLBO | Veldhuisen 1999 | Placebo | NA | NA | NA | 12 weeks |
| PLBO | CASSIS 1995 | Placebo | NA | NA | NA | 12 weeks |
| PLBO | SOLVD-treat 1991 | Placebo | NA | NA | NA | 48 months |
| PLBO | SOLVD-prevent 1992 | Placebo | NA | NA | NA | 37.4 months (mean) |

* Arm excluded from analysis (more common dose available)

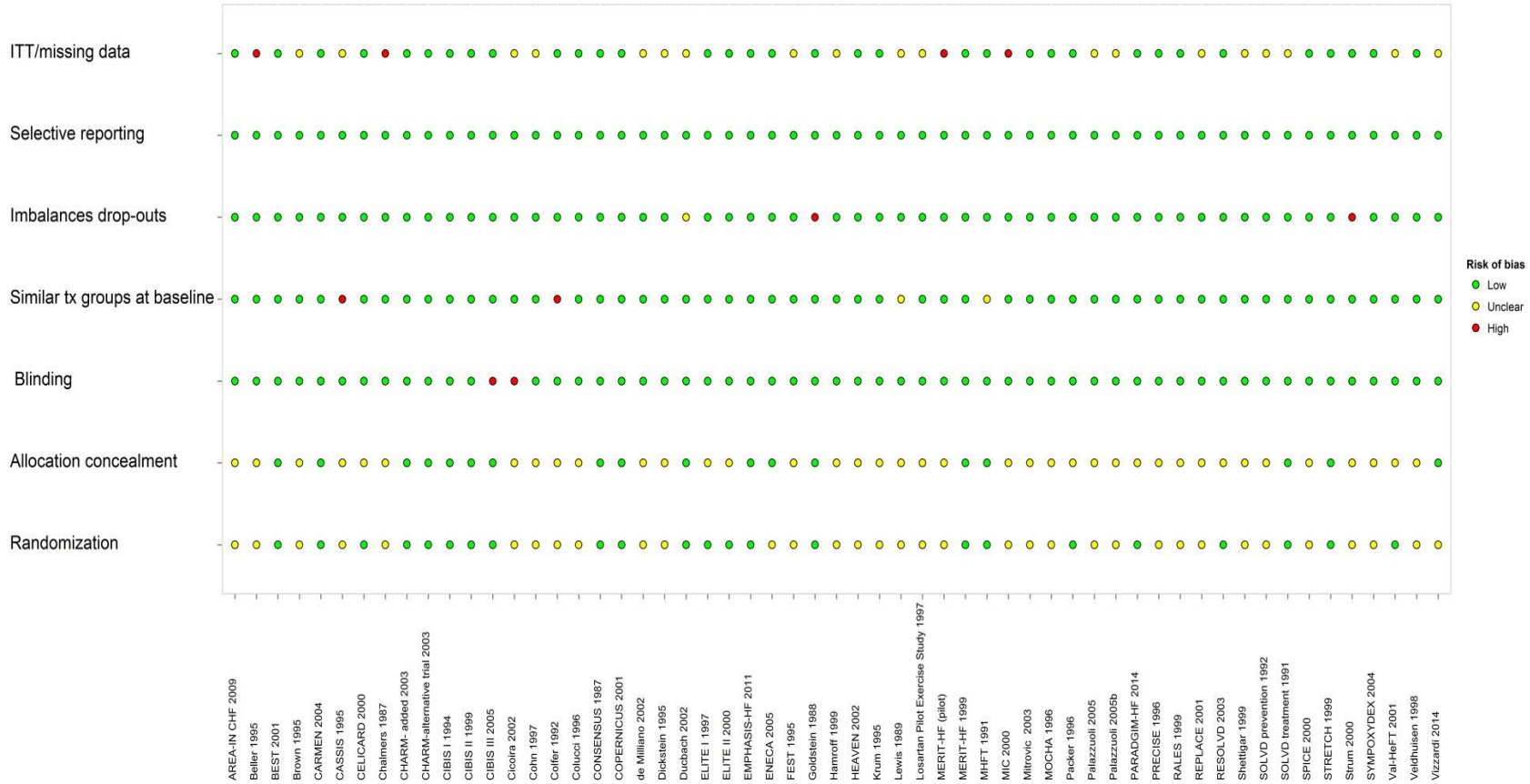
Abbreviations: ACEI = angiotensin-converting-enzyme inhibitor; ARB = angiotensin-II receptor antagonist; ARNI = angiotensin receptor-neprilysin inhibitor; BB = beta blocker; BID = twice daily; mg = milligrams; MRA = mineralocorticoid receptor antagonist; NA = not applicable; NR = not reported; OD = once daily; PLBO = placebo; QID = four times daily; TID = three times daily

**Supplementary Figure 1: Quality assessment results A) Summary by domain, B) Summary by RCT**

**A)**

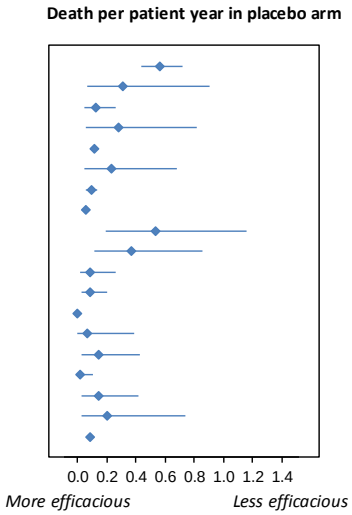


**B)**


ITT/missing data
Selective reporting
Imbalances drop-outs
Similar tx groups at baseline
Blinding
Allocation concealment
Randomization
Risk of bias
Low
Unclear
High
AREA-IN CHF 2009
Beller 1995
BEST 2001
Brown 1995
CARMEN 2004
CASSIS 1995
CELICARD 2000
Chalmers 1987
CHARM- added 2003
CHARM-alternative trial 2003
CIBIS I 1994
CIBIS II 1999
CIBIS III 2005
Cicoira 2002
Cohn 1997
Colfer 1992
Colucci 1996
CONSENSUS 1987
COPERNICUS 2001
de Milliano 2002
Dickstein 1995
Ducbach 2002
ELITE I 1997
ELITE II 2000
EMPHASIS-HF 2011
ENECA 2005
FEST 1995
Goldstein 1988
Hamroff 1999
HEAVEN 2002
Krum 1995
Lewis 1989
Losartan Pilot Exercise Study 1997
MERIT-HF (pilot)
MERIT-HF 1999
MHFT 1991
MIC 2000
Mitrovic 2003
MOCHA 1996
Packer 1996
Palazzuoli 2005
Palazzuoli 2005b
PARADGIM-HF 2014
PRECISE 1996
RALES 1999
REPLACE 2001
RESOLVD 2003
Shettigar 1999
SOLVD prevention 1992
SOLVD treatment 1991
SPICE 2000
STRETCH 1999
Strum 2000
SYMPOXYDEX 2004
Val-HeFT 2001
Veldhuisen 1998
Vizzardi 2014

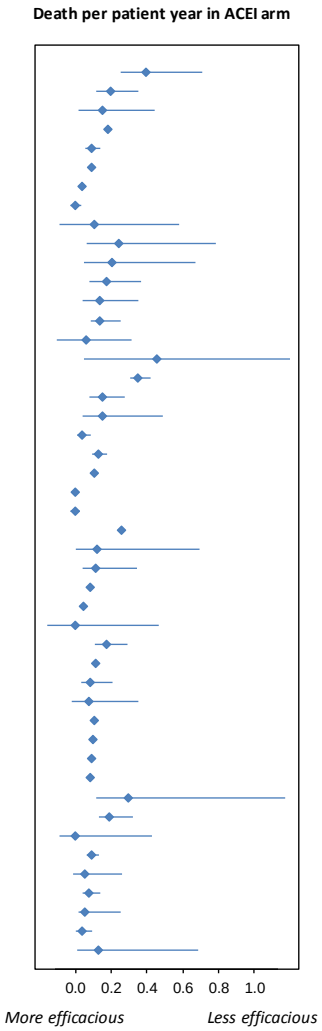
**Supplementary Figure 2: Rates per patient year sorted by publication year and presented by treatment arm for A) Placebo, B) ACEI, C) all other treatment arms**

**A)**



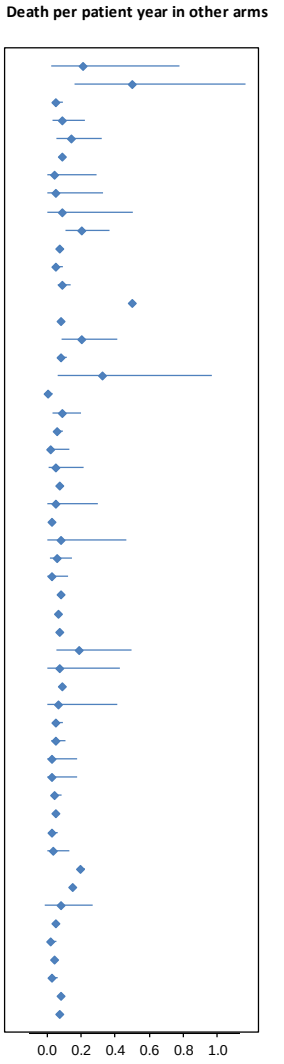

| Tx class | Trial | Follow-up (months) | # randomized | # completers | Person years at risk | Deaths | Rate (per patient year) | 95% CrI low | 95% CrI high |
|---|---|---|---|---|---|---|---|---|---|
| PLBO | CONSENSUS 1987 | 12.0 | 126 | 108 | 117 | 66 | 0.56 | 0.72 | 0.44 |
| PLBO | Chalmers 1987 | 3.0 | 43 | 35 | 10 | 3 | 0.31 | 0.90 | 0.06 |
| PLBO | Goldstein 1988 | 6.0 | 100 | 100 | 50 | 6 | 0.12 | 0.26 | 0.04 |
| PLBO | Lewis 1989 | 3.0 | 43 | 43 | 11 | 3 | 0.28 | 0.82 | 0.06 |
| PLBO | SOLVD treat 1991 | 55.0 | 1284 | 752 | 4667 | 510 | 0.11 | 0.12 | 0.10 |
| PLBO | Colfer 1992 | 3.0 | 58 | 45 | 13 | 3 | 0.23 | 0.68 | 0.05 |
| PLBO | MHFT 1992 | 36.5 | 87 | 74 | 245 | 22 | 0.09 | 0.14 | 0.06 |
| PLBO | SOLVD prevent 1992 | 48.0 | 2117 | 1164 | 6563 | 334 | 0.05 | 0.06 | 0.05 |
| PLBO | CASSIS 1995 | 3.0 | 48 | 42 | 11 | 6 | 0.53 | 1.16 | 0.19 |
| PLBO | Beller 1995 | 3.0 | 63 | 46 | 14 | 5 | 0.37 | 0.85 | 0.12 |
| PLBO | FEST 1995 | 3.0 | 153 | 118 | 34 | 3 | 0.09 | 0.26 | 0.02 |
| PLBO | Brown 1995 | 6.0 | 125 | 74 | 50 | 4 | 0.08 | 0.21 | 0.02 |
| PLBO | RALES (dosing) 1996 | 3.0 | 40 | 40 | 10 | 0 | 0.00 | 0.00 | 0.00 |
| PLBO | Veldhuisen 1998 | 3.0 | 62 | 54 | 15 | 1 | 0.07 | 0.38 | 0.00 |
| PLBO | Shettigar 1999 | 3.0 | 104 | 60 | 21 | 3 | 0.15 | 0.43 | 0.03 |
| PLBO | STRETCH 1999 | 3.0 | 211 | 211 | 53 | 1 | 0.02 | 0.11 | 0.00 |
| PLBO | SPICE 2000 | 3.0 | 91 | 79 | 21 | 3 | 0.14 | 0.41 | 0.03 |
| PLBO | Mitrovic 2003 | 3.0 | 44 | 34 | 10 | 2 | 0.21 | 0.74 | 0.02 |
| PLBO | CHARM-alt 2003 | 42.0 | 1015 | 1015 | 3553 | 296 | 0.08 | 0.09 | 0.07 |

**B)**



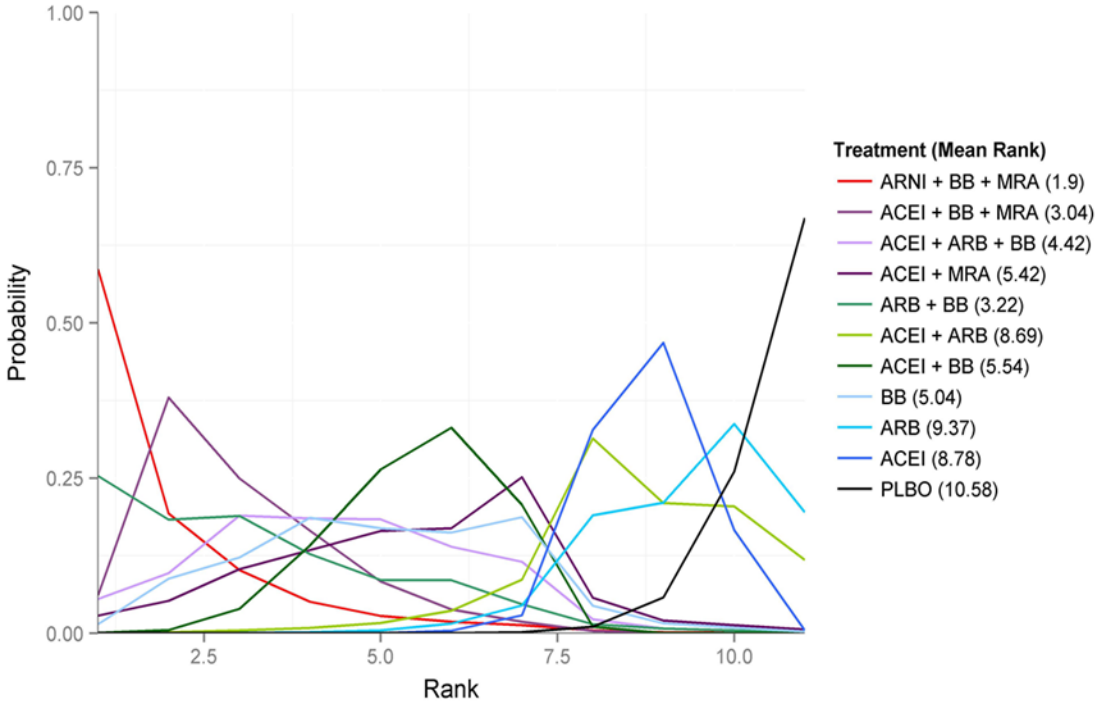

| Tx class | Trial | Follow-up (months) | # randomized | # completers | Person years at risk | Deaths | Rate (per patient year) | 95% CrI low | 95% CrI high |
|---|---|---|---|---|---|---|---|---|---|
| ACEI | CONSENSUS 1987 | 12.0 | 127 | 105 | 116 | 46 | 0.40 | 0.53 | 0.29 |
| ACEI | Chalmers 1987 | 3.0 | 87 | 72 | 20 | 4 | 0.20 | 0.52 | 0.05 |
| ACEI | Goldstein 1988 | 6.0 | 104 | 104 | 52 | 8 | 0.15 | 0.30 | 0.07 |
| ACEI | Lewis 1989 | 3.0 | 87 | 87 | 22 | 4 | 0.18 | 0.47 | 0.05 |
| ACEI | SOLVD treat 1991 | 55.0 | 1285 | 867 | 4933 | 452 | 0.09 | 0.10 | 0.08 |
| ACEI | MHFT 1992 | 40.4 | 83 | 59 | 239 | 22 | 0.09 | 0.14 | 0.06 |
| ACEI | SOLVD prevent 1992 | 48.0 | 2111 | 1942 | 8106 | 313 | 0.04 | 0.04 | 0.03 |
| ACEI | Colfer 1992 | 3.0 | 114 | 98 | 27 | 0 | 0.00 | 0.00 | 0.00 |
| ACEI | CIBIS I 1994 | 26.0 | 321 | 239 | 607 | 67 | 0.11 | 0.14 | 0.09 |
| ACEI | CASSIS 1995 | 3.0 | 51 | 47 | 12 | 3 | 0.24 | 0.72 | 0.05 |
| ACEI | Dickstein 1995 | 2.0 | 58 | 58 | 10 | 2 | 0.21 | 0.75 | 0.02 |
| ACEI | CASSIS 1995 | 3.0 | 48 | 42 | 11 | 2 | 0.18 | 0.64 | 0.02 |
| ACEI | FEST 1995 | 3.0 | 155 | 127 | 35 | 5 | 0.14 | 0.33 | 0.05 |
| ACEI | Beller 1995 | 3.0 | 130 | 105 | 29 | 4 | 0.14 | 0.35 | 0.04 |
| ACEI | Brown 1995 | 6.0 | 116 | 81 | 49 | 3 | 0.06 | 0.18 | 0.01 |
| ACEI | Krum 1995 | 3.5 | 16 | 14 | 4 | 2 | 0.46 | 1.65 | 0.05 |
| ACEI | MOCHA 1996 | 6.0 | 84 | 63 | 37 | 13 | 0.35 | 0.60 | 0.19 |
| ACEI | Packer 1996 | 6.0 | 398 | 398 | 199 | 31 | 0.16 | 0.22 | 0.11 |
| ACEI | PRECISE 1996 | 6.0 | 145 | 145 | 73 | 11 | 0.15 | 0.27 | 0.08 |
| ACEI | Colucci 1996 | 12.0 | 134 | 134 | 134 | 5 | 0.04 | 0.09 | 0.01 |
| ACEI | Cohn 1997 | 6.0 | 35 | 27 | 16 | 2 | 0.13 | 0.47 | 0.01 |
| ACEI | ELITE I 1997 | 11.0 | 370 | 259 | 288 | 32 | 0.11 | 0.16 | 0.08 |
| ACEI | Lang 1997 | 3.0 | 38 | 38 | 10 | 0 | 0.00 | 0.00 | 0.00 |
| ACEI | Veldhuisen 1998 | 3.0 | 60 | 56 | 15 | 0 | 0.00 | 0.00 | 0.00 |
| ACEI | RALES 1999 | 24.0 | 841 | 630 | 1471 | 386 | 0.26 | 0.29 | 0.24 |
| ACEI | Hamroff 1999 | 6.0 | 17 | 13 | 8 | 1 | 0.13 | 0.70 | 0.00 |
| ACEI | MERIT-HF 1999 | 12.0 | 2001 | 1691 | 1846 | 217 | 0.12 | 0.13 | 0.10 |
| ACEI | Shettigar 1999 | 3.0 | 102 | 85 | 23 | 2 | 0.09 | 0.31 | 0.01 |
| ACEI | CIBIS II 1999 | 46.0 | 1320 | 1320 | 5063 | 228 | 0.05 | 0.05 | 0.04 |
| ACEI | Goldstein 1999 | 6.0 | 19 | 16 | 9 | 0 | 0.00 | 0.00 | 0.00 |
| ACEI | MIC 2000 | 6.0 | 26 | 19 | 11 | 2 | 0.18 | 0.64 | 0.02 |
| ACEI | Sturm 2000 | 24.0 | 49 | 20 | 69 | 8 | 0.12 | 0.23 | 0.05 |
| ACEI | ELITE II 2000 | 24.0 | 1574 | 1353 | 2927 | 250 | 0.09 | 0.10 | 0.08 |
| ACEI | CELICARD 2000 | 12.0 | 66 | 39 | 53 | 4 | 0.08 | 0.20 | 0.02 |
| ACEI | REPLACE 2001 | 3.0 | 75 | 75 | 19 | 2 | 0.11 | 0.39 | 0.01 |
| ACEI | COPERNICUS 2001 | 21.0 | 1133 | 953 | 1825 | 190 | 0.10 | 0.12 | 0.09 |
| ACEI | BEST 2001 | 42.0 | 1354 | 1351 | 4734 | 449 | 0.09 | 0.10 | 0.09 |
| ACEI | Val-HeFT 2001 | 27.0 | 2499 | 2499 | 5623 | 484 | 0.09 | 0.09 | 0.08 |
| ACEI | HEAVEN 2002 | 3.0 | 71 | 62 | 17 | 5 | 0.30 | 0.70 | 0.10 |
| ACEI | de Milliano 2002 | 6.0 | 11 | 10 | 5 | 1 | 0.19 | 1.06 | 0.00 |
| ACEI | Dubach 2002 | 12.0 | 15 | 15 | 15 | 0 | 0.00 | 0.00 | 0.00 |
| ACEI | SYMPOXYDEX 2004 | 6.0 | 22 | 21 | 11 | 1 | 0.09 | 0.52 | 0.00 |
| ACEI | CARMEN 2004 | 18.0 | 190 | 133 | 242 | 14 | 0.06 | 0.10 | 0.03 |
| ACEI | Palazzuoli 2005b | 12.0 | 27 | 24 | 26 | 2 | 0.08 | 0.28 | 0.01 |
| ACEI | ENECA 2005 | 11.0 | 126 | 112 | 119 | 7 | 0.06 | 0.12 | 0.02 |
| ACEI | Palazzuoli 2005 | 12.0 | 25 | 22 | 24 | 1 | 0.04 | 0.24 | 0.00 |
| ACEI | CIBIS III 2008 | 6.0 | 505 | 456 | 240 | 32 | 0.13 | 0.19 | 0.09 |

**C)**




| Tx class | Trial | Follow-up (months) | # randomized | # completers | Person years at risk | Deaths | Rate (per patient year) | 95% CrI low | 95% CrI high |
|---|---|---|---|---|---|---|---|---|---|
| ARB | Dickstein 1995 | 2.0 | 56 | 56 | 9 | 2 | 0.21 | 0.77 | 0.02 |
| ARB | Lang 1997 | 3.0 | 40 | 40 | 10 | 5 | 0.50 | 1.17 | 0.16 |
| ARB | ELITE I 1997 | 11.0 | 352 | 287 | 293 | 17 | 0.06 | 0.09 | 0.03 |
| ARB | STRETCH 1999 | 3.0 | 213 | 213 | 53 | 5 | 0.09 | 0.22 | 0.03 |
| ARB | SPICE 2000 | 3.0 | 179 | 148 | 41 | 6 | 0.15 | 0.32 | 0.05 |
| ARB | ELITE II 2000 | 24.0 | 1578 | 1453 | 3031 | 280 | 0.09 | 0.10 | 0.08 |
| ARB | REPLACE 2001 | 3.0 | 77 | 77 | 19 | 1 | 0.05 | 0.29 | 0.00 |
| ARB | HEAVEN 2002 | 3.0 | 70 | 65 | 17 | 1 | 0.06 | 0.33 | 0.00 |
| ARB | Mitrovic 2003 | 3.0 | 44 | 44 | 11 | 1 | 0.09 | 0.51 | 0.00 |
| ARB | RESOLVD 2003 | 6.0 | 126 | 122 | 57 | 12 | 0.21 | 0.37 | 0.11 |
| ARB | CHARM-alt 2003 | 42.0 | 1013 | 1013 | 3546 | 265 | 0.07 | 0.08 | 0.07 |
| BB | CARMEN 2004 | 18.0 | 191 | 134 | 244 | 14 | 0.06 | 0.10 | 0.03 |
| BB | CIBIS III 2008 | 6.0 | 505 | 470 | 244 | 23 | 0.09 | 0.14 | 0.06 |
| ACEI + ARB | Hamroff 1999 | 6.0 | 16 | 13 | 7 | 5 | 0.50 | 0.00 | 0.00 |
| ACEI + ARB | Val-HeFT 2001 | 27.0 | 2511 | 2511 | 5650 | 495 | 0.09 | 0.10 | 0.08 |
| ACEI + ARB | RESOLVD 2003 | 6.0 | 86 | 82 | 39 | 8 | 0.21 | 0.41 | 0.09 |
| ACEI + BB | CIBIS I 1994 | 26.0 | 320 | 245 | 612 | 53 | 0.09 | 0.11 | 0.06 |
| ACEI + BB | Krum 1995 | 3.5 | 33 | 29 | 9 | 3 | 0.33 | 0.97 | 0.07 |
| ACEI + BB | Colucci 1996 | 12.0 | 232 | 232 | 232 | 2 | 0.01 | 0.03 | 0.00 |
| ACEI + BB | PRECISE 1996 | 6.0 | 133 | 133 | 67 | 6 | 0.09 | 0.20 | 0.03 |
| ACEI + BB | Packer 1996 | 6.0 | 696 | 696 | 348 | 22 | 0.06 | 0.10 | 0.04 |
| ACEI + BB | MOCHA 1996 | 6.0 | 89 | 82 | 43 | 1 | 0.02 | 0.13 | 0.00 |
| ACEI + BB | Cohn 1997 | 6.0 | 70 | 66 | 34 | 2 | 0.06 | 0.21 | 0.01 |
| ACEI + BB | MERIT-HF 1999 | 12.0 | 1990 | 1711 | 1851 | 145 | 0.08 | 0.09 | 0.07 |
| ACEI + BB | Goldstein 1999 | 6.0 | 42 | 33 | 19 | 1 | 0.05 | 0.30 | 0.00 |
| ACEI + BB | CIBIS II 1999 | 46.0 | 1327 | 1327 | 5090 | 156 | 0.03 | 0.04 | 0.03 |
| ACEI + BB | MIC 2000 | 6.0 | 26 | 22 | 12 | 1 | 0.08 | 0.46 | 0.00 |
| ACEI + BB | Sturm 2000 | 24.0 | 51 | 28 | 79 | 5 | 0.06 | 0.15 | 0.02 |
| ACEI + BB | CELICARD 2000 | 12.0 | 66 | 48 | 57 | 2 | 0.04 | 0.13 | 0.00 |
| ACEI + BB | BEST 2001 | 42.0 | 1354 | 1349 | 4730 | 411 | 0.09 | 0.10 | 0.08 |
| ACEI + BB | COPERNICUS 2001 | 21.0 | 1156 | 1010 | 1896 | 130 | 0.07 | 0.08 | 0.06 |
| ACEI + BB | Cicoira 2002 | 12.0 | 52 | 46 | 49 | 4 | 0.08 | 0.21 | 0.02 |
| ACEI + BB | de Milliano 2002 | 6.0 | 43 | 39 | 21 | 4 | 0.20 | 0.50 | 0.05 |
| ACEI + BB | Dubach 2002 | 12.0 | 13 | 13 | 13 | 1 | 0.08 | 0.43 | 0.00 |
| ACEI + BB | CHARM-added 2003 | 42.0 | 1272 | 1272 | 4452 | 412 | 0.09 | 0.10 | 0.08 |
| ACEI + BB | SYMPOXYDEX 2004 | 6.0 | 28 | 26 | 14 | 1 | 0.07 | 0.41 | 0.00 |
| ACEI + BB | CARMEN 2004 | 18.0 | 191 | 132 | 242 | 14 | 0.06 | 0.10 | 0.03 |
| ACEI + BB | ENECA 2005 | 12.0 | 134 | 124 | 129 | 7 | 0.05 | 0.11 | 0.02 |
| ACEI + BB | Palazzuoli 2005b | 12.0 | 32 | 30 | 31 | 1 | 0.03 | 0.18 | 0.00 |
| ACEI + BB | Palazzuoli 2005 | 12.0 | 33 | 31 | 32 | 1 | 0.03 | 0.17 | 0.00 |
| ACEI + BB | AREA-IN CHF 2009 | 12.0 | 236 | 236 | 236 | 12 | 0.05 | 0.09 | 0.03 |
| ACEI + BB | EMPHASIS-HF 2011 | 36.0 | 1373 | 1145 | 3777 | 213 | 0.06 | 0.06 | 0.05 |
| ACEI + BB | Vizzardi 2014 | 44.0 | 65 | 65 | 238 | 8 | 0.03 | 0.07 | 0.01 |
| ARB + BB | RESOLVD 2003 | 6.0 | 125 | 108 | 53 | 2 | 0.04 | 0.13 | 0.00 |
| ACEI + MRA | RALES 1999 | 24.0 | 822 | 600 | 1422 | 284 | 0.20 | 0.22 | 0.18 |
| ACEI + ARB + BB | RESOLVD 2003 | 6.0 | 89 | 77 | 38 | 6 | 0.16 | 0.34 | 0.06 |
| ACEI + ARB + BB | CHARM-added 2003 | 42.0 | 1276 | 1276 | 4466 | 377 | 0.08 | 0.09 | 0.08 |
| ACEI + BB + MRA | Cicoira 2002 | 12.0 | 54 | 47 | 51 | 3 | 0.06 | 0.17 | 0.01 |
| ACEI + BB + MRA | AREA-IN CHF 2009 | 12.0 | 231 | 231 | 231 | 6 | 0.03 | 0.06 | 0.01 |
| ACEI + BB + MRA | EMPHASIS-HF 2011 | 36.0 | 1364 | 1142 | 3759 | 171 | 0.05 | 0.05 | 0.04 |
| ACEI + BB + MRA | Vizzardi 2014 | 44.0 | 65 | 65 | 238 | 8 | 0.03 | 0.07 | 0.01 |
| ACEI + BB + MRA | PARADIGM-HF 2014 | 27.0 | 4212 | 4203 | 9467 | 835 | 0.09 | 0.09 | 0.08 |
| ARNI + BB + MRA | PARADIGM-HF 2014 | 27.0 | 4187 | 4176 | 9408 | 711 | 0.08 | 0.08 | 0.07 |

**Supplementary Figure 3: Results of random effect network meta-analysis probability rank for all-cause mortality**



## Supplemental References

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